MEDICAL LIBRARY

APR 17 1947

APRIL, 1947

Vol. 125, No. 4

ANNALS of SURGERY

A Monthly Review of Surgical Science and Practice

Included in This Issue

COMPOUND INJURIES OF THE KNEE JOINT
STUDY II—THE INFECTED KNEE JOINT *by*
Joe M. Parker, and John J. Modlin

STUDIES ON THE ACID DÉBRIDEMENT OF BURNS *by*
Marion B. Sulzberger, Abram Kanof and Rudolf L. Baer

PRIMARY FIBROSARCOMA OF THE LIVER *by*
Thomas A. Shallow and Frederick B. Wagner, Jr.

BACTERIOLOGIC STUDY OF BURN WOUNDS *by*
John L. Langohr, Cora R. Owen and Oliver Cope

J. B. LIPPINCOTT COMPANY

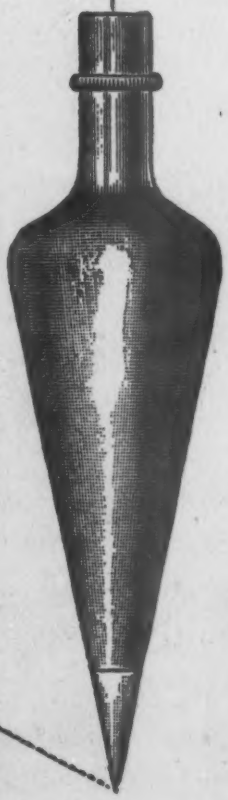
Precision

Of the many types of anesthesia, spinal procedures are the most exacting in their requirements. Because of its pharmacological precision, NEOcaine has demonstrated its fitness for spinal anesthesia over a thirty-year period of clinical use.

In practice, NEOcaine is (1) *always sterile,* (2) virtually flash-soluble in cerebrospinal fluid, (3) stable to epinephrine, (4) rapidly and completely absorbed without irritation and (5) of low toxicity in anesthetic concentrations.

ADMINISTRATION: Employ 1 mg. of NEOcaine per pound of body weight, up to 150 mg. Dissolve crystals with spinal fluid led into the ampoule. Inject slowly with optional barbotage, using a 22 gauge needle. Contraindicated in gastrointestinal perforation, obstruction, peritonitis, severe hypotension, cerebrospinal or dorsal skin disease. Drug idiosyncrasy is rare.

SUPPLIED: Ampoules of 50, 80, 100, 120, 150, 200, 300 mg. of pure procaine hydrochloride. Boxes of 10. For continuous spinal anesthesia, ampoules of 500 mg., individually boxed.



NEOcaine
1917 1946

ANGLO-FRENCH Laboratories, Inc.
75 Varick Street, New York 13, N. Y.

ANNALS OF SURGERY

VOL. 125 APRIL, 1947 No. 4

COMPOUND INJURIES OF THE KNEE JOINT*

STUDY II—THE INFECTED KNEE JOINT

JOE M. PARKER, M.D., AND JOHN J. MODLIN, M.D.

FROM THE DEPARTMENT OF SURGERY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, SAINT LOUIS, MISSOURI

WORLD WAR II has witnessed a significant change in the surgical treatment of severely traumatized and infected knee joints. Because of the dreaded nature of this injury and its complications, the emphasis during the latter part of World War I and the early phases of World War II was placed largely on the saving of life and limb. With the advent of penicillin and the more certain control of infection, a more ambitious goal, the conservation of a functioning joint, has become a possibility. It is to record the feasibility of this constructive approach to the problem that this paper is presented. The conclusions are based on the series of cases seen at the 21st General Hospital during the African, Italian, and French campaigns.

Prior to the general use of penicillin, infection was regarded as inevitable in a considerable number of cases. Treatment was confined to the provision and maintenance of adequate drainage for as long as necessary. At present, the contention of the authors is that established infection can be controlled and a functioning joint obtained if the following conditions can be met: (1) Removal of all actually or potentially devitalized tissue and foreign material which can serve as foci of infection. (2) Control of the residual infection by the systemic and intra-articular use of penicillin. (3) Closure of the knee joint to exclude reinfection from without, and to insure retention of the penicillin. (4) Institution of early, active motion.

Not all infected knee joints can be salvaged, since it may be impossible adequately to débride and yet preserve the joint; or, the soft-tissue loss may be of such magnitude that it is impossible to close the joint. Thus, it becomes impracticable to attempt débridement for the extensively shattered joint which is infected. The infected joint most amenable to the therapy outlined is the one with minimal fracture.

During the African campaign, when the traditional concepts of care of

* From the 21st General Hospital (Washington Univ. Unit).

suppurating arthritis of the knee joint were followed, excellent results were achieved, if judged solely by the fact that there was no death at our hospital attributable to this condition. Furthermore, in no instance was joint suppuration an indication for amputation. However, these results were achieved at the price of a prolonged convalescence and usually a permanent loss of function of the knee joint. The method employed was exteriorization or drainage of the joint by medial and lateral parapatella incisions and prolonged immobilization. While the more fulminating and acute manifestations could thus be controlled, it gradually became apparent that they were followed by a low grade, smouldering infection that eventually led to the development of a stiff joint.

The change of approach in the care of infected knee joints occurred in Italy in the early Spring of 1944. At this time penicillin became generally available, and the concepts of early reparative surgery were developed. These principles, as outlined by Col. E. D. Churchill, were tirelessly disseminated by Major Champ Lyons and Lt. Col. Oscar P. Hampton, Jr., who taught the physiologic and surgical principles that must be observed in the proper use of penicillin and foresaw the possibilities of exploring and closing the infected joints in order to spare the patients the effects of continued suppuration.

During this period, the hospital functioned in the Base, receiving patients directly from Evacuation Hospitals within two to eight days of wounding. It served in a similar capacity later, in France, although evacuation there was not always as prompt. A total of 244 penetrating and perforating wounds of the knee joint were treated. Of these, 29 developed clinical infections of the knee joint.

Clinical Manifestations of Infected Knees.—The campaigns in Italy and France have provided a very unusual opportunity for study of the problem of suppurative arthritis of the knee, as 29 cases have been seen, and 15 of these have been subjected to operation. These experiences have led to the conclusion that, in general, three stages or degrees of suppuration may be seen in knee joints: acute, subacute, and chronic. Unless the process is arrested, however, all lead to the same end—destruction of the joint surfaces. Of these stages, the last, the chronic joint suppuration, is by far the most subtle, and is most likely to escape diagnosis.

(1) Acute suppuration of the knee joint is not a common complication of war wounds. There have been instances, however, from penetrating wounds. The clinical picture is that of marked systemic reaction, with high fever, leukocytosis, prostration, and excruciating pain on motion of the knee. The knee is red, swollen, and very tender. A joint with fulminating infection is usually greatly distended. The wound may show the escape of seropurulent or purulent fluid, the amount depending on the ease with which the fluid has been escaping from the joint through the wound.

(2) The subacute, suppurating joint is the one most frequently seen. The symptoms are not so severe as in the acute type. Fever may be recorded between 102°F. and 103°F. The pulse rate is slightly accelerated. The knee is swollen and tender. Redness and tenderness are not so marked as in the

acute, fulminating joint. There is pain on motion, a very important sign. If left without treatment, the subacute joint may develop into the acute, fulminating pyarthrosis. Case history No. 1, under "Supplement," is submitted to illustrate the points of definition of the subacute suppurating joint.

(3) The chronic suppurating joint is likely to escape diagnosis because the symptoms are low-grade. Prolonged daily fever of perhaps only 99°F. to 99.6°F. is recorded, and there usually persists a slight acceleration of the pulse. The knee joint is tender and motion causes pain, again, a most valuable sign. The wound itself fails to heal and there is an escape of purulent material from sinuses leading to the joint. Unless watched for, this drainage may be so small in amount that it may go undetected. The chronically infected knee may be

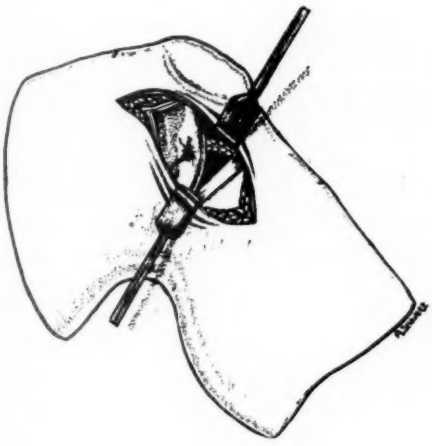


FIG. 1-A

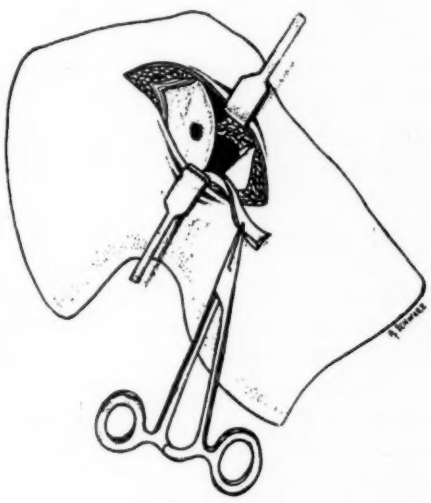


FIG. 1-B

FIG. 1.—(A) Septic knee joint with extension of previously débrided wound to permit adequate visualization of interior of joint. Note penetrating wound of medial femoral condyle.

(B) Same joint after curettage and débridement of condylar defect and detachment of anterior portion of medial meniscus.

the result of persistence arising from inadequate treatment of the subacute joint. It is the type of reaction that develops when the joint is left open because soft-parts are insufficient to close-off the joint cavity. As the name implies, it is a late stage of a continuing suppuration.

In addition, most of these patients are anemic from continual blood destruction and require repeated transfusions. They exhibit weight loss and cachexia. If the problem is complicated by wounds of other systems or organs, the diagnosis may be difficult. A typical example of the chronic suppurating joint is submitted as Case No. 2 in the "Supplement."

Gross Pathology of the Different Stages.—(1) In the acute, septic joint, the periarticular structures are edematous and the synovium is thick and

injected. Fibrin accumulations with purulent degeneration within the joint are common. A careful search within the joint will usually reveal the devitalized area wherein the infection had its origin. In the early, acute, suppurating knee joint, the menisci appear viable, but because of their normal avascularity and lack of resistance to infection, it is impossible to be certain of their continued viability.

(2) In the subacute joint, which is usually seen and operated upon somewhat later, degeneration of the menisci may be evident. This is the type of suppurating joint in which it is common to see retained foreign bodies, with articular damage. When the meniscus is devitalized, it becomes dull, yellowish, and soft. Usually, the meniscus on the side of the wound is the first to undergo degeneration.

(3) The chronically suppurating joint is, as the name implies, an older process, with definite progressive destruction of its most susceptible structures. The menisci are generally found degenerated, and the areas of contact between the tibial and femoral condyles may be in various stages of erosion, with loss of the cartilaginous surfaces. The same process may be noted between the patella and the femoral condyles. The articular cartilage in contact with the devitalized meniscus may also be degenerated. These various degrees of destruction were described by Phemister in 1924. In the chronic stages, the hyperemia of the more fulminating process is lacking. There may be partial obliteration of the joint cavity by fibrous adhesions. The chronic stage is an indolent process associated with the gradual destruction of articular cartilage and later involvement of the underlying bone.

Treatment of the Infected Knee.—The primary assumption made by the authors in the treatment of infected joints is that the joint defends itself best as a completely closed cavity. The first goal, then, is to restore the joint as a closed space. Furthermore, penicillin can be kept in the greatest concentration within the joint if the latter is water-tight. Next, an attempt is made to eliminate all dead tissue within the joint. Thus, reliance is placed on the inherent ability of viable structures with adequate blood supply to resist the action of invasive bacteria, aided to some extent by penicillin.

Without doubt, good results have been obtained in the past by arthrotomy and drainage of the joint. It is possible, however, that it was the ability of the synovium to seal itself off rapidly that led to the favorable outcome, and that joints which did not cease draining shortly developed cartilaginous damage.

Actually, all the infected joints that were the result of relatively minor injuries, revealed undébrided, damaged cartilage or bone, and this was felt to be the origin of the infectious process. To quote an axiom of reparative surgery: "Penicillin will not sterilize devitalized tissue." The natural resistance of undamaged knees to withstand the trauma of exposure and exploration is impressive. It would seem that infection rarely develops in the knee that has no devitalized tissue to serve as the nidus for infection. The one exception to this is the joint constantly contaminated by an infected fracture site.

Once the infectious process is started, however, the various structures within the joint possess definite but different powers of resisting the necrotizing

effect of suppuration. In turn, these devitalized structures sustain and prolong the infection. Of all the structures within the joint, the menisci are the least able to resist this necrotizing action. After the menisci, the articular cartilage, especially where contact between condyles occurs, is most apt to necrose.

Based on these facts, the approach to treatment of suppurating knee joints has been directed toward excising the menisci, performing a thorough and meticulous excision of all detached, devitalized cartilage and bone, and removing all foreign bodies found within the joint. The joint is then closed, and

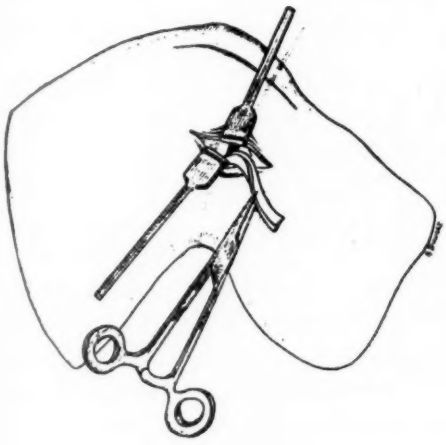


FIG. 2

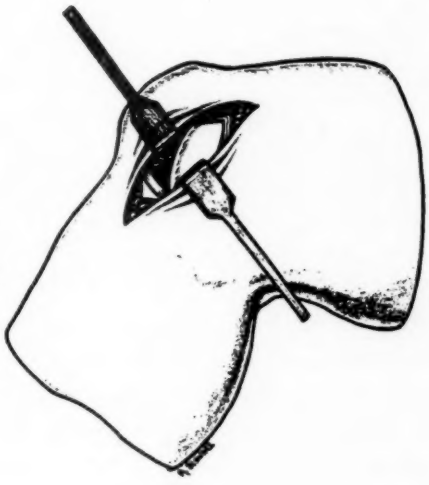


FIG. 3

FIG. 2.—Showing posteromedial "Henderson" approach for removal of entire medial meniscus. This is not always used. The medial collateral ligament is carefully retracted.

FIG. 3.—Lateral parapatella incision to permit visualization of lateral portion of joint and excision of lateral meniscus.

penicillin is instilled. Both the synovium and skin are closed in the arthrotomy incision. As much of the meniscus as possible is removed. A short posterior incision on the medial side will enable one to excise almost the entire medial meniscus. A recent publication by Smillie indicates that the best functional result is obtained by excising the entire meniscus.

Details of this secondary débridement vary somewhat in the different stages of the infected knee:

(1) In the acute septic knee, the menisci usually have not had time to degenerate, and it is impossible to judge their continued viability. Because of the acuteness of the process, it has been thought wise to excise both menisci through medial and lateral parapatella incisions. Although this portion of the operation might be classified as a prophylactic procedure, it is resorted to in an effort to arrest established virulent infection by removing potentially devitalized

structures and such nonresistant tissues as may have already been irreparably damaged by local conditions within the joint.

(2) In the subacute joint, which is usually seen and operated upon somewhat later, degeneration of the menisci may be evident. This is the type of suppurating joint that is most commonly seen when foreign bodies and devitalized articular cartilage remain within the joint. It is the type that responds well to arthrotomy and excision of the menisci. If left untreated, the end-results are almost universally bad. If the meniscus on the side opposite the wound appears normal, it may be left *in situ*. The amount of additional trauma to the joint produced by the removal of the normal appearing meniscus must be weighed against the danger of leaving it within the joint to degenerate subsequently. With minor degrees of reaction within the joint, it seems probable that there is less danger of the viable-appearing meniscus undergoing degeneration at a later time.

(3) With the increased age of the process, the mechanical difficulties of operative intervention are increased. In chronically infected knees, the areas of incision ordinarily are marked by the presence of sinuses, arising from either old incisions or the débrided wound. As previously stated, the operative treatment must be adequate to remove all questionable tissue within the joint. Since the menisci are generally found degenerated at this stage, they must be excised completely. The articular cartilage must be curetted to good bone in those areas where it is necrotic and in the process of degeneration. After the joint has reached this stage of disintegration, it seems likely that it will never be completely painless and that the patient will most probably require resection and fusion of the knee. However, it is possible to arrest the process at this stage and to obtain some motion of the joint, by thorough débridement. Case No. 2 under "Supplement," was a patient who had destruction of the contact surfaces of both the medial and lateral condyles of the tibia and femur. Following excision of the menisci and curettage of the destroyed cartilage, the superficial wounds drained for a few days, but when heard from some ten months after return to the Zone of Interior, he had healed and stayed healed, with 10° to 15° of motion of the knee. Those patients who have not developed destruction of the articular cartilage may be expected to obtain good motion and essentially normal knees. The removal of the completely devitalized meniscus seems to give no lasting disability. It is true that no complete follow-up is available, but the condition of the patients at the time of evacuation would lead one to this conclusion.

Analysis of Operative Results.—Infection, the most dreaded of knee complications, was seen in 29 of the entire series of 244 compound injuries of the knee joint. The criteria used for judging a knee to be infected were, generally, those signs and symptoms described under the heading "Clinical Manifestations of Infected Knees." These cases also showed purulent exudate within the joint, and sometimes the culture was positive for staphylococci or streptococci. Most of these joints had had penicillin instilled, and the absence of

bacteria on culture may possibly be attributed to this fact, as well as the lack of facilities for extensive anacrobic analysis.

Of the 29 infected joints, 15 were explored, using as a basis for treatment the principles of reparative surgery outlined under the heading "Treatment of the Infected Knee." In 14 of the 15 explored patients, the infectious process was eliminated by débridement, including excision of the menisci, closure of the joint, and instillation of penicillin. The one patient who did not respond to the treatment continued to suppurate because of the presence of osteomyelitis of the femoral condyle. Both menisci were removed in eight of the 15 arthrotomies. The lateral meniscus alone was removed in five instances, and the medial meniscus was excised as part of the operative procedure in two cases.

Thirteen of the 15 explored knees subsided promptly, and had some degree of painless motion when evacuated to the Zone of Interior. One of the remaining two patients subsided after a few days and has remained healed for ten months. The one real failure is discussed at more length later.

Of the 29 infected joints, 14 were not subjected to operation. The 14 "unexplored" patients were judged not amenable to arthrotomy and débridement of the joint. Thirteen of the 14 cases had extensively comminuted fractures within the joint and débridement was considered impracticable.

When the comminution is extensive, or when large fragments are broken free and lie within the joint, operative revision becomes a formidable procedure. It has been found that débridement of a comminuted joint will result in operative removal of so much of the joint or articular surface that the articulation can no longer be functional. Furthermore, with removal of the fragments as a part of the secondary débridement, later resection for fusion will result in excessive shortening of the extremity.

Occasionally, in the severely fractured and infected knee, resection of the joint must be done early in order to save life. If the infection permits, on the other hand, it is better to resort to the old type of treatment, and simply drain the joint. Usually in this type of case the soft-tissue damage is so extensive that open drainage is easily maintained. The extremity is immobilized in a plaster hip spica. By such a method, the patient generally can be spared the most serious systemic consequences of a pyarthrosis. By localizing the infection to the joint space, one hopes that the multiple, loose, comminuted fragments of the condyle will become revascularized and solidify. If it is possible to postpone the resection and fusion until such time as this occurs, the operation may be carried out with minimal shortening of the leg.

Four of the infected knee joints regarded as inoperable, insofar as attempting to save the joint was concerned, were subjected to early resection. This type of resection is done frequently by French surgeons and consists, in brief, of excision of the cartilaginous portions of the femur and tibia and approximation of the denuded cancellous ends of the two bones. The French surgeons, with whom we have talked, give Ollier credit for having popularized this operation. It is technically an easy procedure. Usually, the patient with a severe suppurating joint, exhibiting cachexia, weight loss, and anemia,

responds well to this type of therapy. The four patients who were subjected to resection are reviewed briefly.

TABLE I

Total number of compound knee joints treated	244
Total number of infected knee joints	29
Number possibly infected but not definite	8
Total secondarily débrided by method described	15
Cases judged irreparable (not explored)	14
Irreparable cases which were resected and fused	4

An American soldier had loss of the lateral condyle of the tibia and extensive loss of soft-parts over the lateral side of the knee. It was impossible to close the joint even by a flap. This patient was blind, and it was thought unwise to delay resection because of the possibility of severe infection which might necessitate amputation and deprive him of such proprioceptive powers as the fused leg might afford.

An American soldier had a partial resection of a completely destroyed knee joint as a part of his primary care in the Evacuation Hospital. As a further complication, he had a dead extremity on the opposite side, secondary to popliteal artery division. The resection of the joint was done to control severe local infection.

The third patient was one with severe fracture, loss of soft-parts, and a virulent superimposed infection. The joint was resected early in an attempt to control the infection. Unfortunately, he developed osteomyelitis of the resected tibia and a spreading infection up the posterior fascial planes of the thigh. The limb was then amputated. This man had extensive periosteal stripping of the tibia, and this was felt to be a large factor in his lack of resistance to bone infection.

The fourth resected case was one with minimal fracture who was seen so late that the joint was destroyed. His prolonged suppurative process had debilitated him to such an extent that immediate resection seemed indicated. His history is presented in more detail in the "Supplement," Case No. 3, since it shows the hazards of inadequate early care of compound injuries of the knee.

TABLE II

Type of Case	Operation		Disposition to Zone of Interior	Total
	Resection	Amputation		
Irreparable because of fracture and infection	1	0	5	6
Irreparable because of fracture, infection and open joint	2*	2	3	7
Irreparable because of prolonged infection but with minimal fracture	1	0	0	1
Total irreparable, infected joints	4*	2	8	14

* One was later amputated.

Thirteen of the 14 cases judged unsuitable for attempt at operative revision had severe fractures which complicated the operative procedure to such an

extent that a functional joint could not be expected. The one patient with irreparable joint damage but minimal fracture has been discussed. It is impossible to save all knee joints in warfare because of the frequent serious nature of the complicating fracture and avulsion of soft-parts. Seven of the 14 irreparable knees had such extensive loss of soft-parts that flap closure was either impossible or resulted in failure when tried.

Two amputations were performed in the series of 14 and, in addition, one patient's leg was amputated after the operation of resection. The infection in this case was not controlled by resection. It was the only one in which resection failed to control infection and the amputation was resorted to as a life-saving measure.

Another case coming to amputation was a patient with a previous amputation below the knee and with an open joint and severe condylar fracture. When first inspected, he had a dirty, necrotic knee joint, and reamputation was performed in the lower thigh. One patient, with thigh amputation for gas gangrene, was not considered an amputation for uncontrolled infection of the knee joint.

The remaining eight patients with infected, open joints were relatively afebrile and comfortable when returned to the Zone of Interior for definitive care and probable fusion. They were treated according to the generally accepted methods for suppurating joints, and all will probably have stiff knees, or may end up with operative fusion. In every case, the joints were open and draining.

Eight of the cases (Table I) are listed as possibly infected, but it was impossible to judge accurately. Occasionally, the infection may be so low-grade that it escapes detection. This is apt to be the case more often in the highly comminuted joint. Sometimes, the infectious process is eliminated spontaneously. Due to the tactical situation, a few cases were evacuated before they could be definitely assessed.

The results in those patients upon whom operative intervention was tried in order to arrest suppuration are tabulated in Table III.

TABLE III

Total compound joints	244
Total infected joints	29
Total joints explored for infection	15
Successful elimination of infection by operation	14
Unsuccessful elimination of infection by operation	1

In all, 15 patients with suppurative arthritis of the knee joint were subjected to arthrotomy, débridement, and closure. Fourteen of these cases were successfully relieved of the infectious process within the joint. The response to operative intervention was usually prompt and gratifying. The effusion subsided rapidly so that in two or three days it was often difficult to aspirate anything from the joint before instilling penicillin. Periarticular swelling persisted for a few days, but the temperature gradually fell as the

effusion subsided. Motion of the knee was encouraged as soon as pain and tenderness permitted. Lack of pain was found to be a very good index of the proper time to institute motion. Almost all the patients had a fair range of painless motion when evacuated.

The one patient upon whom the operative treatment failed had a wound of the popliteal space. Débridement and formal arthrotomy had been done in the forward area, but an anterior approach had not revealed the foreign body or the articular cartilage damage. When he reached the Base, he had a subacute suppurative arthritis. Shortly after admission, the foreign body was removed, and the area about the damaged cartilage was débrided. The joint continued to suppurate and was reopened in order to remove the menisci and curette the area on the medial posterior femoral condyle. At this operation it was observed that the area of osteomyelitis had enlarged. After this second procedure, he continued to run fever, and the joint was painful and distended. It was necessary to resort to the open joint method of drainage. Foreign bodies in the posterior part of the joint are frequently difficult to find, and surgeons called upon to treat those injuries should be well-acquainted with the anatomy and surgical approaches to the knee joint, recently reviewed by Abbott and Carpenter. The foreign body and cartilage damage could have been easily reached at the time of débridement had a posterior, or Henderson, incision been used.

FIG. 4.—Anterior view of joint showing sutured medial and lateral parapatella incisions. (Synovium also sutured.) Posteromedial sutured wound not shown.

Table IV is a summary of the 15 patients upon whom operative intervention was undertaken.

Case 9 presents some interesting details. This patient had an infected bullet wound, which in our experience is rare. Also, he seemed to have an infected knee joint, without cartilaginous damage. However, in repeated notes, it was stated that he had little, if any, pain on motion of the knee, and the diagnosis of suppurative arthritis was questionable. He did have prolonged fever and pus was aspirated from the suprapatella region. The joint was finally explored by a lateral approach, and a walled-off abscess of the suprapatella pouch was encountered. Since the knee was contaminated by the procedure, the lateral meniscus was removed to lessen the hazards of infection.

Case 15 was evacuated before the full extent of the response to treatment could be judged. The patient was one with acute manifestations and was still slightly febrile when evacuated. It is possible that he should not be included in this series.

DISCUSSION.—Admittedly, the criteria for established infection within the knee joint are not absolute, since it was impossible to obtain carefully controlled laboratory studies on all the patients treated. Positive cultures were obtained from most of the knees, however, although clinical abstracts fre-

TABLE IV

Case No.	Missle	Bony Injury	Days After Wounding Until Arthrotomy or Primary Care	Secondary Care	Findings and Procedure	Result
1.	SF*	Pen. fract. lat. condyle of femur and incomplete fract. of patella	Formal explor. Arthrotomy	10	Infected patella curetted. Excision medial meniscus and curette lat. condyle of femur	Healed
2.	SF	Shaft of femur, with with extension into knee	Formal explor. Arthrotomy	12	Infected fracture reduced. Excision of both menisci	Healed
3.	SF	Pen. injury of post. med. fem. condyle, with retained foreign body	Formal explor. arthrotomy	21	Osteo. about foreign body. Excision of both menisci and curettage of the medial femoral condyle	
				31 (reoperated)	Osteo. progressive. Joint left open	Septic
4.	SF	Fract. lat. cond. of femur	Débrided. No formal arthrotomy	10	Excise part of loose lateral condyle. Excision of lat. meniscus	Healed
5.	SF	Fract. lateral condyle of femur	Débrided. No F.A.	7	Excision of part of lat. condyle. Excision lateral meniscus	Healed
6.	SF	Pen. fract. med. condyle of femur	Débrided. No F.A.	10	Excision of both menisci. Débride and curette condyle	Healed, 20° of motion
7.	SF	Lateral condyle of femur about half avulsed	Débrided. No F.A.	8	Ant. cruciate severed. Lat. Condyle of femur loose and removed. Excision of both menisci	Healed
8.	SF	Fract. lower one-third femur, with secondary compound knee	Débrided. Joint inspected	45	Both menisci necrotic and excised. Articular cartilage curetted at points of contact	Healed
9.	Bullet	Minimal cartilage injury to femoral condyle	Débrided. No F.A.	8	Excision lat. meniscus. Had a localized abscess in suprapatellar pouch	Healed
10.	SF	Commin. fract. of upper tibia. Chip fract. of patella	Débrided. No F.A.	6	Curette patella. Excise both menisci. Slide-flap to close joint	Healed
11.	SF	Fract. med. tibial condyle. Retained foreign body	Débrided. No F.A.	13	Remove F.B. excision lateral meniscus. Curette tibial plateau	Healed
12.	SF	None	Débrided. No F.A.	13	Excision of medial meniscus. Removal F.B. in suprapatellar pouch	Healed
13.	SF	Medial tibial condyle	None	6	Excision lat. meniscus curette tibial condyle. Remove foreign body	Healed 60° of motion
14.	SF	Upper tibia	Débrided.	60	Excision of both degenerated menisci. Curette all areas of articular cartilage contact	Healed
15.	Not a battle casualty	None	None	3	Grease and dirt in compound injury sustained in auto accident. Excision both cartilages	Healed

* Shell fragment.

quently have failed to record the report. The clinical evaluation based on temperature, pain on motion, local tenderness, gross appearance of the joint, the character of the joint fluid and, most important, inspection of the interior of the joint, must be accepted as the basis of the report.

Criteria for arrest of the joint infection have been established. Most of the patients have been followed long enough to demonstrate some degree of painless motion, freedom from fever and general systemic improvement.

The excision of the menisci would seem to be an innocuous procedure, insofar as later function of the uninfected joint is concerned. Whether the altered conditions of suppuration within the joint at the time of meniscectomy may affect the ultimate functional result is not known.

In the acute suppurative joint, when the menisci still appear viable, removal of these structures may be questioned. The decision to remove them was made after observing the necrotic menisci in the more chronically infected joints. There can be no doubt that a meniscus is very susceptible to suppuration within the joint. The acute suppurative joint is a serious and formidable problem that calls for the most vigorous measures. Temporizing and trusting that the menisci will remain viable, have not been a part of this operative scheme.

It is recognized that some of the patients, although spared the hazards of suppuration, will have disability that may require future reconstructive procedures. Those with partial loss of a condyle, or with serious ligamentous injury of the knee, may even have to have their knee joints fused. In these patients it can be claimed only that they have been spared the debilitation and hazards of chronic suppuration. Some of the "cured" knees have cartilaginous defects in important weight-bearing areas that may predispose to difficulty. In spite of these facts, it is our belief that the patients have been given the best chance to obtain a serviceable knee joint.

SUPPLEMENT

Case 1.—American officer wounded, August 16, 1944, in Southern France by shell fragments. Due to the tactical situation at the time, he was evacuated to a hospital ship without treatment. On the ship, wounds of the right forearm and thigh were débrided the day after injury. The missile that had penetrated the right knee was not disturbed.

He reached the 21st General Hospital, August 22, 1944, (six days after wounding), with a swollen, tender knee and a temperature of 102°. Motion was not excessively painful, but the joint was hot. Roentgenograms showed a chip-fracture of the patella and a foreign body embedded in the articular surface of the tibia. A formal arthrotomy was performed under a cuff tourniquet on the day of admission. The joint was explored through a medial parapatella incision. There was seropurulent fluid in the joint. The foreign body was extracted, and the defect in the tibial condyle curetted. The medial meniscus was found partly torn, and it was excised. An area of cartilaginous injury on the lateral side of the medial femoral condyle was trimmed. The synovium and skin were closed, with the injection of 20,000 units of penicillin.

The postoperative course was smooth, with rapid subsidence of fever. Motion was started eight days after arthrotomy. He had 60° of motion when discharged to the Zone of Interior.

Case 2.—American soldier, wounded at Anzio Beachhead, February 20, 1944, by shell fragments. He sustained a penetrating wound of the left thigh, with a comminuted fracture of the femur. The left knee was compounded at the fracture site. The wound was débrided 20 hours after injury at an Evacuation Hospital and a plaster hip spica applied. He arrived at the Base, February 23, 1944, fairly comfortable. On February 25, 1944, the encasement was removed and the extremity placed in skeletal traction. The wounds were not sutured because they did not look clean. On March 6, 1944, (two weeks after wounding) the temperature was 102°F. A diagnosis of a subacute infected knee was made. According to the accepted policies at that time, he was treated conservatively, and the fracture site drained; this, in turn, drained the knee joint. He continued to run a low grade fever. Repeated drainage of the fracture site was performed. In each instance, the knee joint was shown to connect with the fracture site and to contain pus.

Finally, on April 6, 1944, just six and one-half weeks after wounding, the joint was opened widely in order to test the new concepts of reparative surgery on a case of established knee joint infection. The program of penicillin plus reparative surgery had been introduced some two weeks before this time at this hospital.

At operation, both menisci were found devitalized. The points of contact between articular surfaces of tibia and femur, and also between femur and patella, were found in various stages of autolysis. All devitalized tissue was excised and curetted. The joint was then closed and penicillin instilled. The fracture site was fixed by four screws and drained dependently. Because of the multiple incisions and the superficial infection, it was impossible to follow with certainty the state of infection within the joint. However, in retrospect, it seems that it subsided promptly, since only blood could be obtained from the knee joint on repeated aspirations. Instilled penicillin did not leak from the joint. Incisions were almost fully healed when he was discharged, and ten months later, reports from the Zone of Interior indicated that healing was complete.

Case 3.—American soldier, wounded in France, October 31, 1944, by shell fragments, sustained multiple wounds of the chest, abdomen, both arms, and both legs. He was treated at a Field Hospital 30 hours after injury by resection of a segment of the jejunum and primary anastomosis; débridement of all wounds and irrigation of a penetrating wound of the right knee with the installation of penicillin.

A pyarthrosis of the right knee developed. Thirteen days after injury he was transferred to an Evacuation Hospital, where, on the day following admission, he was subjected to formal arthrotomy and the foreign body removed. On November 23, 1944, the joint was explored for the second time, and the medial meniscus removed. On November 27, 1944, he was transferred to the 21st General Hospital where conservative therapy was tried because the joint was open and draining. It became evident that the patient was losing ground. He was extremely emaciated, with an anemia that required repeated blood transfusions. There was loss of appetite and progressive weight loss.

On December 10, 1944, under ether anesthesia, an arthrodesis of the right knee was performed, excising the patella and resecting the cartilaginous portions of the tibia and femur. A few days following resection he began to gain weight, and continued to improve until evacuated January 30, 1945.

The bony damage was slight, consisting of a penetrating type of injury to the femoral condyle.

SUMMARY

1. An analysis of 29 infected knee joints is presented. These cases represent the total infected knee joints in a series of 244 compound injuries of the knee.

2. Because of the high incidence of complications resulting from the use

of traditional methods of therapy in suppurative arthritis of the knee joint, a more active plan of treatment was developed.

3. The clinical manifestations and gross pathology of the acute, subacute, and chronic stages of infectious arthritis of the knee are presented.

4. An active operative approach to these cases is outlined, with the elimination of all devitalized and potentially devitalized tissue within the joint, the closure of the synovial cavity and skin, and the local use of penicillin.

5. Arrests of the infectious process was obtained in 14 of 15 cases operated upon according to these principles.

6. Case histories are presented.

REFERENCES

[1] Abbott, L. G., and Carpenter, W. F.: Surgical Approaches to the Knee Joint. J. Bone and Joint Surg., **27**, 277, 1945.

[2] Churchill, E. D.: Surgical Management of the Wounded in the Mediterranean Theater at the Time of the Fall of Rome. ANNALS OF SURGERY, **120**, 268, 1944.

[3] Lyons, Champ: Penicillin Therapy of Surgical Infections in the United States Army. J. A. M. A., **123**, 1007, 1943.

[4] Phemister, D. B.: Changes in the Articular Surfaces in Tuberculosis and in Pyogenic Infections of Joints. Amer. J. Roentgen., **22**, 1, 1924.

[5] Smillie, I. S.: Observations on the Regeneration of the Semilunar Cartilages in Man. Brit. J. of Surg., **31**, 398, 1944.

SURGICAL MANAGEMENT OF GUNSHOT WOUNDS OF THE PELVIC VISCERA AND THEIR LATE COMPLICATIONS*

LT. COL. GEORGE BENTON SANDERS, M.C.
LOUISVILLE, KY.

AND

MAJOR IAN G. HODGE, M.C.
LANCASTER, PA.

FROM THE SURGICAL SERVICE, VAUGHAN GENERAL HOSPITAL, HINES, ILLINOIS

PERFORATING GUNSHOT WOUNDS of the pelvis are among the most baneful of war injuries. Their high mortality and morbidity are due to the presence of important hollow viscera of several systems which are closely packed into this bony cavity, any, or all, of which may be irreparably damaged by the passage of a missile. To this may be added the shock of the bony damage itself which, although not of a degree comparable with that attending fracture of the bones of the lower extremities, nevertheless, remains an important added insult.

Statistical studies in clinical surgery are often misleading. Nowhere are they more so than in the surgery of warfare. As Morgan has most aptly stated: "It is unwise to draw too many conclusions from the study of wounded at the Base, since the Forward Surgeon alone knows of his failures and disappointments; the survivors tell only of the triumphs."

It is well, therefore, to bear this in mind when reviewing the following statistics.

According to Sandrey and Mogg, who surveyed a large series of cases from World War I, the incidence of bladder wounds in warfare is comparatively rare; namely, about one in every 3,000 or 4,000 battle wounds. However, according to these authors, wounds of the bladder constitute as much as 5 per cent of all abdominal wounds. The same authors give the incidence of associated pelvic fracture in cases of bladder wounds as over 50 per cent, and state that associated injury to the rectum occurs in over 33 per cent of bladder wounds. In a series of 53 cases of wounds of the bladder from the World War I, surveyed by Fullerton, the incidence of associated pelvic fracture was given as 42 per cent. Changing technics of warfare, and especially the evolution of the land mine as a weapon of defense, has, according to first reports, increased the incidence of injury to the pelvis and its viscera, especially during certain phases and campaigns of the recent war. Table I, based on necessarily incomplete reports, is only an approximation of what is to be expected from the completed statistical surveys of this conflict.

Wounds of the ureter are said to be statistically rare. In World War I, only two cases of ureteral wounds were reported from a study of a large number of abdominal wounds in the British Expeditionary Force. Young was able to discover only four cases of ureteral injury in a similar survey made on casualties from the American Expeditionary Force. Most authors, British and

* Presented at the Surgical Conference, Sixth Service Command, Chicago, Illinois, 1945.

American, who have discussed the subject, admit, however, that the incidence must be much higher since many cases are either overlooked, or die of more severe associated visceral injuries. Kimbrough in a recent study of 237 consecutive injuries to the genito-urinary tract has reported eight cases of ureteral injury. It must be emphasized again, however, that these figures were compiled from the hospital records of rear echelon installations and are, therefore, subject to the misleading influences of sampling and selection.

TABLE I

INCIDENCE OF ASSOCIATED BONY PELVIC INJURY IN WOUNDS OF THE PELVIC VISCERA

Location	Fracture of Pelvis
Deep urethra	20%
Bladder*	45–60%
Colon and rectum	55%
Combined injuries, both systems	65%

* Wounds of bladder, with or without bony injury, are associated with wounds of the colon or rectum in 45–70% of the cases.

The viscera most often injured in compound gunshot fractures of the pelvis fall naturally into four main groups: First, organs of the gastro-intestinal tract; namely, the cecum, sigmoid, rectum and, lastly, the terminal ileum, which is injured so often, like an innocent bystander in all types of gunshot injuries in this region. Second, the genito-urinary organs; the deep urethra, bladder, and juxtavesical portions of the ureters. Third, combined injuries of the above two systems, which occur in the following order of frequency: rectum and urethra, rectum and bladder, sigmoid and bladder, and sigmoid and left ureter. (Cecal and right ureteral injuries are rare, although one was encountered on the Surgical Service of this hospital.) Fourth, injuries to the great vessels and nerves of the pelvis.

Of these injuries due to gunshot wounds, those of the deep urethra, bladder, rectum, and sigmoid, although *usually* caused by the missile, may be produced by indriven bony fragments from the pelvis, in which case they are almost always extraperitoneal. The remainder, including the combined injuries, are nearly always due to the missile itself. In the present war the missiles causing these injuries are more often fragments of high explosive shell or bomb casing than rifle or machine gun bullets, in the ratio of about 3 to 1. The former show a high percentage of retention within the tissues of the pelvis, the latter often make a complete perforation and exit from the body.

PRIMARY SURGICAL MANAGEMENT

Proper surgical management of these injuries in the forward areas is exceedingly important, not only for the saving of life, but for the reduction of morbidity and the prevention of distressing complications which will require extensive and elaborate surgery later. Adherence to, or deviation from, fundamental surgical principles is directly reflected in morbidity figures and in the necessity for future surgery involving sacrifice of tissues and organs.

In general, it may be said that the early surgical care of these cases embraces the following four cardinal principles: Recognition; repair; diversion; and drainage.

Recognition.—It is, by now, a surgical aphorism that every wound of the buttock, perineum, upper thigh, or hip, should be considered as penetrating the abdomen unless it can be conclusively demonstrated otherwise. Even at celiotomy, however, early recognition, not only of the presence, but of the type, extent, and multiplicity of injury may be exceedingly difficult, especially in extraperitoneal injuries of the rectum and ureter. Reconstruction of the track of the missile should aid in detection of concealed damage, the most valuable manifestation of which is extravasation of blood or urine. The possibility of progressive infarction of the intestinal wall, with subsequent perforation distinct from the main rent, should always be kept in mind, as emphasized by Shaw Dunn, in 1917.

In practically all cases of gunshot wounds of the pelvis, an attempt should be made to pass a catheter into the bladder. Cystography and cystoscopy have been advocated, but are often not feasible in forward areas, and are not without danger. Excretory urography, if available, is valuable, especially in the diagnosis of ureteral injury.

Repair.—In wounds of the colon, exteriorization is the procedure of choice, but is not always feasible in the case of injury to the fixed portions of the colon. Suture repair of urinary and colonic defects is of the utmost desirability in wounds of the bladder and of colonic segments that cannot be exteriorized. The fear of later bowel stenosis should not inhibit thoroughness in repairing colonic defects unsuitable for exteriorization since a complementary proximal colostomy should always be done.

In urethral injuries, primary suture is desirable only if the lesion is readily accessible. With injuries to the deeper portions of the urethra, approximation of the torn ends by combined manipulation, both retrograde and from below, with immobilization of the segments by a catheter splint, is the simplest and most desirable treatment. As a general rule, primary suture repair is not often practical for the ureteral injuries of warfare. However. if the injury involves the distal end of the ureter, an immediate ureterovesical transplant is recommended. In higher ureteral injuries, if recognized early, a simple closure which does not unduly constrict the ureter is sometimes feasible.

Diversion.—Efficient diversion of the fecal or urinary flow is an essential corollary. In wounds of the cecum and ascending colon, ileocolostomy, with resection or repair of the damaged right colon, is the ideal advocated by many, which is rarely achieved, while exteriorization, slightly less than ideal but still efficient, is too infrequently attempted and too often inadequately done. Cecostomy, which has been most frequently employed, has proved very disappointing in the prevention of late complications in the cases that have been reviewed at this hospital, and its value of an emergency measure seems to leave much to be desired. Wounds of the transverse colon are easily exteriorized. In injuries of the left colon, exteriorization in the form of a proper colostomy seems to be the procedure of choice, and often, of necessity. Failing this, and especially in

wounds of the pelvic colon too low to exteriorize, diversion seems to us most ideally obtained by means of an adequate defunctioning colostomy of the Devine or double-barrelled spur-type, made no lower than the transverse colon, a point which, although originally mentioned by Lockhart-Mummery and Cuthbert Wallace, has been insufficiently stressed to date. In injuries of the urinary tract either at, or distal to, the bladder, a suprapubic cystotomy should always be done. It is of the utmost importance that the suprapubic drainage tube emerge from the bladder at or near the junction of the anterior and superior aspects of that organ and that the direction the tube follows through the abdominal wall be upwards and anteriorly so that it emerges at a point midway or higher, between the umbilicus and symphysis pubis.

Cutaneous ureterostomy or nephrostomy have been advised as emergency measures in certain ureteral injuries but, to date, we have seen no cases in which this was done or in which we believe such treatment was indicated primarily.

Drainage.—Adequate free drainage of all extraperitoneal injuries, actual and potential, and of all tissue planes opened-up by dissection is an absolute "must." In the repair of injuries involving the bladder, the extravesical spaces must be adequately drained. In injuries to the urethra, perineal drainage should be instituted if there is any suspicion of extravasation. With ureteral lesions, adequate and free drainage of the retroperitioneal tissues by means of a soft rubber tube, capable of maintaining urinary drainage, should be instituted and the drain allowed to remain in place until urinary drainage has ceased. In colonic injuries, the omission of drainage, especially of extraperitoneal injuries, most frequently results in the lethal "colon septicemia" described in the first World War, or, if the patient survives this, troublesome abscesses and complex fecal fistulae develop. The most difficult problems in drainage are those associated with colonic injuries near the bottom of the rectovesical pouch in which a decision must be made whether to drain transperitoneally by the suprapubic route or extraperitoneally from below *via* the perirectal space.

LATE COMPLICATIONS

The late complications of these injuries of the pelvic viscera with which we are most concerned in general hospitals in this country, include: Obstruction; fistula; stricture; urinary tract lithiasis; and infection. Of these, the management of fistulae, whether fecal, urinary, or combined urinary-fecal, interests us most at this time. A detailed discussion of the problems and methods of attack on such fistulae is not germane to this report. Certain principles will be presented which have seemed of importance to us concerning the surgical management of persistent fecal fistulae from the large bowel, and of urinary-fecal communications or fistulae. The management of the other complications listed is similar to that employed in civil practice and has been dealt with adequately by many writers on the subject.

Fecal Fistula.—We feel strongly that older methods of dealing with persistent fecal fistula, involving dissection and excision of the track down to the

opening in the bowel, which is then closed through what is often an inadequate operative incision, are unsatisfactory. With the advent of succinylsulfathiazole, a more radical transperitoneal attack on the origin of the fistula in the bowel wall, including excision of the indurated margins of the bowel defect, resection of the involved colonic segment if necessary, and thorough layer-suture of the bowel, as in an elective anastomosis, can be safely undertaken, and has been our personal choice in 15 cases. Adequate mobilization of the bowel is imperative, neglect of which may result in failure of the closure. Reinforcement of the suture line with an omental flap or graft is highly desirable. The fistulous track itself may then be either excised, curetted and packed, or even left to obliterate spontaneously.

TABLE II

Fecal Fistula:

(1) Spontaneous closure the rule if:
- (a) Fistula is tortuous.
- (b) Fistula does not traverse bone, abscess or granulomatous mass.
- (c) Efficient defunctioning colostomy is present proximally.
- (d) Bowel defect is not large.
- (e) Obstruction is absent distally in the bowel.

If above favorable conditions are lacking, direct attack often must be made to close colonic defect by suture.

(2) Direct attack on fistula necessitates:
- (a) Efficient debacterialization of involved colon—(succinylsulfathiazole, and/or favorably placed and adequately defunctioning colostomy).
- (b) Freedom from obstruction distally in the large intestine.
- (c) Freedom from active infection adjacent to fistula.

Urinary-Fecal Communications.—In combined injuries to the gastro-intestinal and genito-urinary tracts, urinary-fecal communications commonly develop which present interesting problems to the surgeon and urologist. With careful analysis, a rational, staged-attack may be planned, with, in many instances, resulting conservation of tissues and organs, and the cure of the fistula without undue danger to the patient.

It has appeared to us that the primary consideration in preparing these patients for surgical cure of such a complex fistula is the establishment of a thoroughly efficient defunctioning colostomy well proximal to the involved segment of bowel. Hardly less important is the provision and maintenance of adequate urinary decompression or drainage.

The choice and location of the colostomy for fecal diversion is important. We prefer a Devine-type of colostomy made in the right transverse colon, for all lesions distal to the splenic flexure. A completely divided type of colostomy, with the two limbs brought out of the abdomen at a short distance from each other, is fully as efficient as the Devine colostomy, and permits a more anatomic reconstruction of bowel and abdominal wall at the time of closure. Tangential or loop-colostomies are not efficient exclusion procedures. In the case of fistulae involving the right hemicolon, we feel that an end-to-side ileotransversecolostomy is preferable to cecostomy.

With the establishment of fecal diversion and adequate urinary drainage, many urinary-fecal communications appear to close spontaneously, but will

reopen upon restoration of the fecal stream. In two of our cases, closure of a sigmoid colostomy resulted in the reopening of previously closed ureterocolic and vesicocolic fistulae. Permanent cure resulted in each after the establishment of a Devine colostomy followed by transperitoneal closure of the communication.

In two other cases from our series, fistulae between the right ureter and ascending colon apparently closed following end-to-side ileocolostomy. The permanence of closure was never estimated because extensive urinary infection, lithiasis, and renal damage necessitated right nephrectomy in both. In these two cases, both admitted to our Service with such severe renal damage that the necessity for nephrectomy was obvious, the problem arose as to whether to do the nephrectomy first, or to exclude the right hemicolon by ileocolostomy as a preliminary measure. In each case, a communication existed between the ureteropelvic junction and the ascending colon. Feeling that the nephrectomy incision would involve the colonic defect, it was decided to perform ileocolostomy as a preliminary measure in each. Spontaneous closure of the communications apparently resulted, and subsequent nephrectomy was performed without incident and without the feared wound infection. Permanent cure of the external portion of the fecal fistula, however, required right hemicolectomy in each case.

Damage to the ureter is usually so extensive in ureterocolic fistulae, that intractable ureteral stricture results even after successful closure, making nephrectomy mandatory. For this reason, it is usually the procedure of wisdom not to attempt to preserve the involved kidney but to accomplish the cure of the fistula by nephro-ureterectomy. Our experience with this interesting complication is, admittedly, limited to three cases, in two of which nephro-uretrectomy was done. In the third case, however, which will be presented later, it was possible to eradicate the fistula by a transperitoneal attack, and to preserve the kidney.

TABLE III

Urinary-Fecal Communications:

(1) Requirements for closure:
- (a) Adequately defunctioning colostomy favorably placed.
- (b) Adequate diversion and/or drainage of urinary flow.
- (c) Freedom from distal obstruction in both systems.

Under the above conditions spontaneous closure of the urinary portion of the defect often occurs, but reopening will occur if adverse conditions of infection and/or obstruction supervene later.

(2) Fecal end of communication usually needs direct surgical attack even after spontaneous closure of urinary portion. Requisites for efficient and permanent operative closure of colonic portion of fistula are:
- (a) Freedom from active infection (abscess, cellulitis) adjacent to fistula.
- (b) Defunctioned, debacterialized bowel.
- (c) Direct suture of colonic defect, or resection of involved colonic segment.
- (d) Interposition of omental or peritoneal flap if possible.

If a direct attack is necessary on either the ureter or the bladder to close such a fistula, adequate urinary drainage must be carefully maintained. In the case of ureteral lesions, a temporary ureteral splint in the form of a ureteral catheter may be used for the first few days if it is watched carefully. Adequate drainage of soft-tissue planes for possible leakage must be maintained.

PRESENTATION OF CASES

Of some 106 cases of perforating wounds of the abdominal viscera admitted to the surgical service of Vaughan General Hospital there were 45 cases of gunshot wounds of the pelvic viscera requiring reparative surgery at this hospital. Of the latter, 14 were associated with compound fracture of the bony pelvis (Table IV).

Of six cases with ureteral injury admitted to this hospital, two were associated with compound fracture of the pelvis, a high incidence, since in warfare usually the upper ureter is the site of injury and the bony pelvis escapes damage. Of these six cases, only two were discovered at overseas installations, one at the Base, 2.5 months after wounding; the other at the Front at the time of the primary operation, 13 hours after wounding. The remaining four were disclosed during routine preoperative studies on the Surgical Service of this hospital, three to four months after the initial combat injury.

TABLE IV

SITES OF INJURY IN 14 CASES OF COMPOUND PELVIC FRACTURE, WITH VISCERAL DAMAGE DUE TO MISSILE

Location of Bony Injury	Location of Visceral Injury
1. Ala of right ilium	Ascending colon
2. Ala of right ilium	Cecum
3. Ala of left ilium	Terminal ileum, sigmoid
4. Sacrum	Bladder, sigmoid, terminal fifth of left ureter
5. Sacrum	Rectum and bladder
6. Ala of right ilium	Ascending colon, cecum, terminal ileum
7. Ala of left ilium	Left sciatic nerve
8. Sacrum	Terminal fourth, left ureter
9. Ala of left ilium	Sigmoid, terminal ileum, jejunum
10. Ala of left ilium	Ileum
11. Sacrum	Rectosigmoid
12. Horizontal rami, both pubes	Penile and membranous urethra
13. Ascending and descending rami, left ischium	Anus and rectum
14. Right femoral head and acetabulum	Bladder

Of these 14 cases, the following five have been selected as showing most clearly some of the important points in surgical treatment which have already been discussed.

ILLUSTRATIVE CASE REPORTS

Case 1.—H. Z., age 25, was wounded in Germany by a sniper bullet which entered the abdomen *via* the left lower quadrant and exited through the left iliac region causing in transit a compound fracture of the left ilium, multiple perforations of the jejunum and ileum, and a complete transection of the sigmoid colon. At operation, 11 hours later, the perforations in the ileum were closed, ten inches of jejunum were resected with end-to-end anastomosis, and the severed ends of the sigmoid were brought out of the abdomen, as a colostomy, through a stab incision in the left lower quadrant. Postoperative course was uneventful except for drainage and sloughing of tissue from a sinus in the débrided wound of exit.

On admission to Vaughan General Hospital, June 8, 1945, the patient presented the following: A well made sigmoid colostomy in the left lower quadrant. An inflammatory

mass, the size of a grapefruit in the left iliac fossa, completely occluding the distal limb of the colostomy. A large fistulous track, passing through the mass and through a defect in the ala of the left ilium, with its external opening in the wound of exit, its internal opening in the distal limb of the colostomy about one inch below the skin surface. Pressure on the mass caused thick pus to well-out of both ends of the fistula (Fig. 1).

Course in Vaughan General Hospital: On July 3, 1945, a Devine colostomy was made in the right half of the transverse colon, followed seven days later by wide incision and drainage of the mass in the left iliac fossa. Shortly thereafter, the mass decreased rapidly and had practically disappeared 16 days postoperatively. The fistula remained open. Since it was wide, short, and traversed bone close to its source in the bowel, direct attack was thought necessary for permanent cure of the fistula. After resection of the involved segment of colon, with end-to-end anastomosis, a procedure particularly adapted to a bowel defunctioned by a Devine colostomy, permanent healing resulted. The Devine colostomy was closed four weeks later without incident.

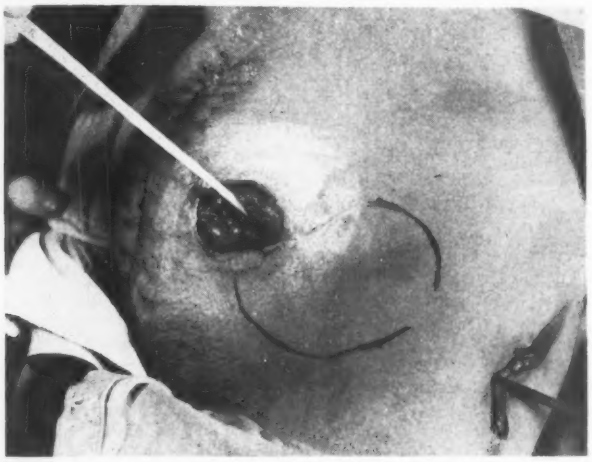


FIG 1.—Case 1: The abscess in the iliac fossa is outlined on the skin. The skin discoloration over the abscess can be seen. Pointers are in the internal and external openings of the fecal fistula which traverses the ala of the left ilium. The colostomy is rotated 90°.

COMMENT.—This case illustrates the inadequacy of a defunctioning colostomy placed close to the site of original injury in the bowel, and emphasizes the point that elective colostomy, in cases of injury to the pelvic bowel and viscera, should be made no lower than the transverse colon. In this case, of course, the exteriorization colostomy in the sigmoid was the choice of necessity and not of election, but it might have been wiser at the time to complement this with a proximal transverse colostomy.

Case 2.—V. N., age 21, was wounded in action in the Philippines by a sniper bullet on April 2, 1945. The bullet entered the abdomen anteriorly through the right lower quadrant near the midline, tracked backward and slightly upward, and exited in the right flank posteriorly, causing a compound fracture of the ala of the right ilium and a perforating wound of the ascending colon in transit. At operation, four hours later, a débridement of the wound of exit was performed, the abdomen was opened through a lower right rectus incision, excising the wound of entrance, and the rent in the extraperi-

toneal portion of the ascending colon was closed by suture. The site of injury was drained through the right flank and a simple cecostomy was done. Postoperative course was fairly uneventful, but the patient developed a fecal fistula at the site of injury to the colon which drained intermittently through both the wound of exit and the drainage wound in the right flank. The patient began to have daily bowel movements per rectum about one month after operation. The cecostomy continued to drain a moderate amount of semiliquid feces.

The patient was admitted to Vaughan General Hospital, May 12, 1945, at which time he presented the following: A simple cecostomy in the right lower quadrant draining a small amount of feces intermittently. Two fecal fistulae, one in the right lumbar region, the other in the right flank, passing through the ala of the right ilium, and both communicating with each other at their common origin in the ascending colon.

Large rubber catheters could be passed into the colon with ease through both fistulous openings. Barium enema showed the defect in the colon as a large tent-like process of bowel which had been drawn into the defect in the ilium. On July 19, 1945, a thorough closure of the cecostomy was done extraperitoneally. The peritoneum was then opened, the ascending colon and cecum mobilized and the colon was detached from the ilium, revealing an extraperitoneal rent in the bowel, about 5 cm. in its longest diameter, which had been drawn in purse-string fashion into a large bony defect in the ilium about the size of a silver dollar. There was evidence of chronic osteomyelitis of the ilium. The bowel defect was repaired with a two-layer suture, a flap of omentum was reflected over the suture line and interposed between the bowel and the bony defect, and the area was thoroughly drained extraperitoneally through the right flank.

Postoperative course was uneventful, with the patient ambulatory on the first postoperative day, normal bowel movements the second postoperative day, regular house diet the third postoperative day. On the eighth postoperative day, the patient developed signs and symptoms of partial small bowel obstruction near the ileocecal junction, and a mass, the size of an orange, could be felt in the right lower quadrant. He was again subjected to operation and an abscess containing about 60 cc. of creamy pus was drained extraperitoneally in the right lower quadrant. Exploration of the interior of the abscess cavity revealed no communication with the bowel but traced its origin back to the area of osteomyelitis in the right ilium. After this, the patient did exceedingly well, continued to have normal bowel movements by rectum; the abscess cavity closed promptly, but the patient continued to drain a moderate amount of pus from the sinus in the right iliac region overlying the area of osteomyelitis. The fecal fistulae, however, remained closed. Consequently, about one month later, a sequestrectomy of the right ilium was performed, removing four moderate-sized bony fragments and excising the surrounding diseased bone. Complete healing of the wound was obtained 12 days later. During the past six months, he has suffered no recurrence of infection or drainage (Figs. 2, 3, 4, A and B).

COMMENT.—This case demonstrates the inadequacy of cecostomy as a diverting mechanism for perforations of the right colon. An excellent demonstration of the fact that a fecal fistula traversing bone cannot be expected to heal spontaneously.

Case 3.—G. O., age 35, was wounded in Italy by a fragment of high explosive shell on June 3, 1944. The fragment perforated the sacrum just to the right of the midline, tracked anteriorly and to the left and did not exit. At celiotomy, done 24 hours later, four perforations of the rectosigmoid and one of the bladder were found and sutured and a proximal sigmoid colostomy was performed. An indwelling urethral catheter was inserted into the bladder and catheter drainage of the bladder was continued for the following month. After removal of the catheter, the patient had no urinary difficulty.

One month later, he was admitted to Vaughan General Hospital in good condition.

FIG. 2.—Case 2: The fracture site in the right ilium is poorly shown.

I. V. pyelograms demonstrated only dilatation of the lower two-thirds of the left ureter and failure of visualization of the terminal 4 cm. or the left ureter. There was no hydronephrosis. Shortly after admission the patient developed left ureteral colic and at about this time, urinary drainage into the distal loop of the colon was demonstrated and corroborated by the injection of indigo-carmine. Cystoscopy and retrograde urography revealed a stricture of the left ureter in its terminal portion, with fairly advanced left hydronephrosis and hydroureter. Three stones were disclosed in the left ureter just above the stricture. Under conservative management, with ureteral catheter drainage and repeated dilatation of the ureter, all stones were passed and the hydronephrosis receded. The sacral sinus of entrance, which had drained intermittently up to this point, was injected with lipiodol and connection with both rectosigmoid and left ureter was

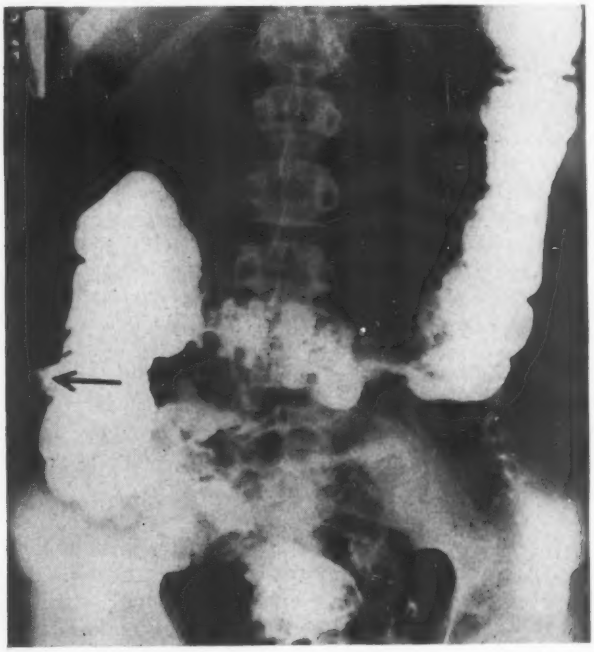
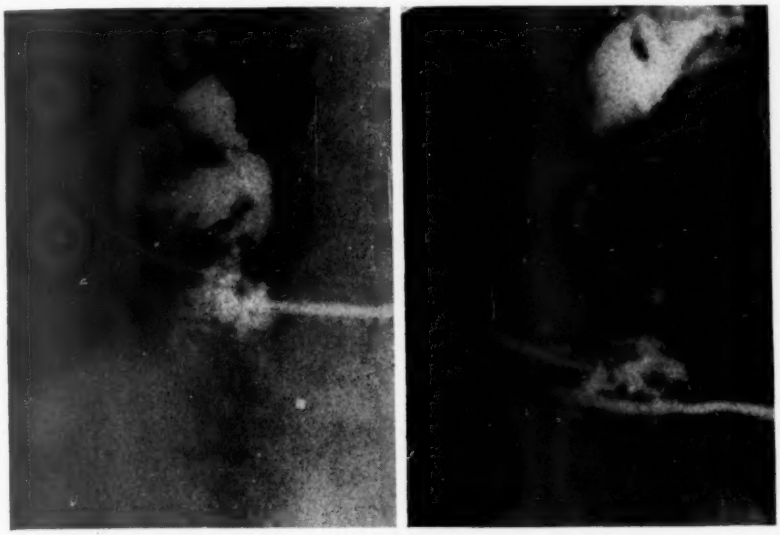


FIG. 3.—Case 2: Barium enema, showing colonic origin of fecal fistulae, one of which traverses ala of right ilium.

demonstrated. A subsequent period of two months of conservative management ensued, during which time the patient's general condition improved remarkably, he gained 25 pounds in weight and the sacral sinus ceased to drain. At this time, all studies indicated closure of the ureterosigmoid and sacral fistulae. After an additional eight weeks of waiting, the sigmoid colostomy was closed. For two weeks thereafter, the patient's convalescence was uneventful. At the end of this time, however, the sacral sinus reopened and drained pus. Studies revealed the reopening of the urinary-fecal communication. A Devine colostomy was then done in the right half of the transverse colon. Shortly after this, the sacral sinus again ceased to drain. One month later, studies revealed closure of the urinary-fecal communication, but the sacral sinus could still be demonstrated communicating with the rectosigmoid. On April 17, 1945, the pelvis was explored transperitoneally, and the rectosigmoid was found to be adherent to the anterior wall of the



A B

FIG. 4.—Case 2: Two views of lipiodol injection of both fecal fistulae, showing persistence despite cecostomy. Note approximation of the two catheters introduced through the two divergent external fistulae, meeting at common origin of the fistulae in the ascending colon.

sacrum and to the juxtavesical portion of the left ureter. A small tent-like process of bowel wall was drawn into the defect in the bone. The rectosigmoid was thoroughly mobilized and peeled off the sacrum and left ureter, disclosing a small rent in the posterior wall of the bowel and exposing the outer coats of the ureter. The lumen of the ureter was not opened in the dissection. The rent in the colon was carefully closed and oversewed, and a pedicle flap of omentum was interposed between the bowel and the sacrum and ureter.

The patient's postoperative course was uneventful, the sinus closed thoroughly and permanently, subsequent studies revealed little evidence of ureteral stricture and no evidence of hydronephrosis, infection, or lithiasis. On June 22, 1945, the Devine colostomy spur was crushed and the fecal stream reëstablished. Closure of the persistent tiny stomas of the Devine colostomy was done under local anesthesia four weeks later. For the past nine months, all studies have failed to demonstrate the recurrence of any fistulous opening, and the patient is in excellent condition, having gained 55 pounds, in all, during

FIG. 6.—Case 3: Lipiodol injection of sacral opening of ureterosigmoid fistula, showing sigmoid and ureteral connections. This incomplete pyelogram was obtained by lipiodol injected solely through the sacral opening. Note ureteral calculus just above stricture in left ureter.

FIG. 5.—Case 3: Retrograde pyelogram, showing degree of hydronephrosis, secondary to stricture, and ureterosigmoid fistula.

this period. Recent pyelograms show a normal kidney, pelvis and ureter on the left, with the exception of a slight narrowing at the site of the former fistula. There is no urinary tract infection as far as can be determined (Figs. 5, 6 and 7).

COMMENT: The ureteral injury was overlooked at the primary operation. Here is a typical instance in which the making of a colostomy below the transverse colon, in a case of pelvic injury, has interfered with subsequent

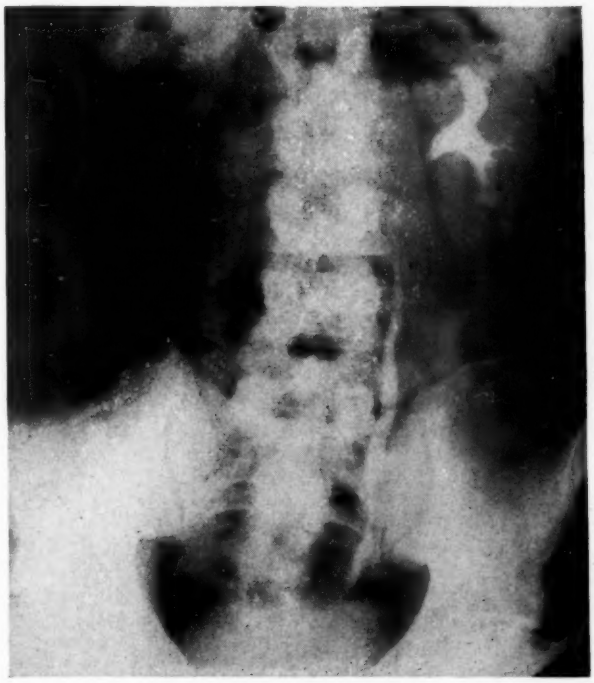


FIG. 7.—Case 3: Retrograde pyelogram done after operative cure of the ureterosigmoid fistula.

reparative surgery. This case demonstrates very well that fecal fistulae traversing bone do not heal spontaneously and, also, that with proper deflection of the fecal stream, the urinary component of a urinary-fecal fistula tends to close spontaneously.

Case 4.—A. K., age 21, was struck by a fragment of high explosive shell on January 29, 1945, which entered the left iliac region, tracked through the ala of the left ilium and penetrated the abdomen, where it was retained in the extraperitoneal tissues of the pelvis. A conservative débridement of the wound of the hip was done, the abdomen opened and a large extraperitoneal hematoma of the left iliac fossa was evacuated. Fearing that the blood supply of the distal colon was impaired, a proximal sigmoid colostomy was done. A fragment of shell was removed from the pelvis but a similar fragment retained in the tissues of the left iliac region was not recovered. Shortly after operation, the presence of a partial left sciatic nerve palsy was discovered.

The postoperative course was somewhat stormy, but the patient was evacuated to the United States and admitted to Vaughan General Hospital on March 27, 1945. On admission, the patient was extremely emaciated, cachectic, and suffering from marked anorexia. He was running a hectic type of temperature and presented in addition to the partial sciatic palsy on the left; a large draining sinus of the left iliac region; and chronic osteomyelitis of the left ilium, with a large (3x4-cm.) sequestrum visualized roentgenologically in the ala of the left ilium. A large abscess cavity was discovered in the pelvis which communicated with the sinus in the left iliac region. After preliminary supportive measures, patient was operated upon, April 12, 1945, at which time

FIG. 8.—Case 4: Lipiodol injection of pelvic abscess through iliac sinus. Note retained fragment of shell-casing, large sequestrum in ala of left ilium.

an incision was made parallel to the crest of the left ilium and about two inches below it, encircling and removing the sinus track. The sequestrum, which involved the margin of the greater sciatic notch, and which lay against the left sciatic nerve and iliac vessels, was removed along with a handful of pulped necrotic bone. The pelvic abscess cavity was then easily entered through the bony defect and evacuated. A large rubber tube drain was inserted through the rectum into the most dependent portion of the cavity which lay against the posterolateral rectal wall. Immediately after operation, the patient noted that he could move his left foot and leg much more freely than before and in the subsequent seven days, most of the residual findings of the sciatic nerve palsy disappeared.

The patient's postoperative course was essentially uneventful, his appetite returned promptly, his fever dropped in 24 hours and remained normal, and he began to gain rapidly in weight and strength. With irrigations through the tube, the cavity closed rapidly and became obliterated in approximately 14 days. On July 19, 1945, after the

patient had been ambulatory for a month and a half, the colostomy was closed, and the remaining fragment of shell was removed from the left iliac region. At present there is only a slight trace of residual sciatic palsy, consisting of minimal atrophy and weakness in the musculature of the leg and thigh. Recent roentgenograms of the left ilium show no evidence of residual osteomyelitis and suggest rapid bony regeneration. All sinuses have been closed for some time (Figs. 8 and 9).

FIG. 9.—Case 4: Roentgenogram of pelvis taken three months after surgical drainage of pelvic abscess through rectum, sequestrectomy, and removal of shell fragment. Residual lipiodol remains from previous injection. Iliac sinus has been healed for six weeks. Note absence of osteomyelitis and beginning bony regeneration in ala of ilium.

COMMENT: Obviously, the primary débridement of the wound of entry and the drainage instituted for the intrapelvic hematoma were inadequate. At the primary operation, with the abdomen open, it should have been relatively easy thoroughly to drain the hematoma extraperitoneally.

Case 5.—H. W., age 30, was wounded by a fragment of high explosive shell on March 31, 1945, which entered the perineum just to the left of the anus, tracked upward along the left side of the rectum and lodged in the left sacral mass at the level of the promontory. At operation, eight hours after the injury, a débridement of the wound of entrance was done, the abdomen was opened and the pelvis explored. No injury to the rectum or bladder was noted but there was evident retroperitoneal hemorrhage. A

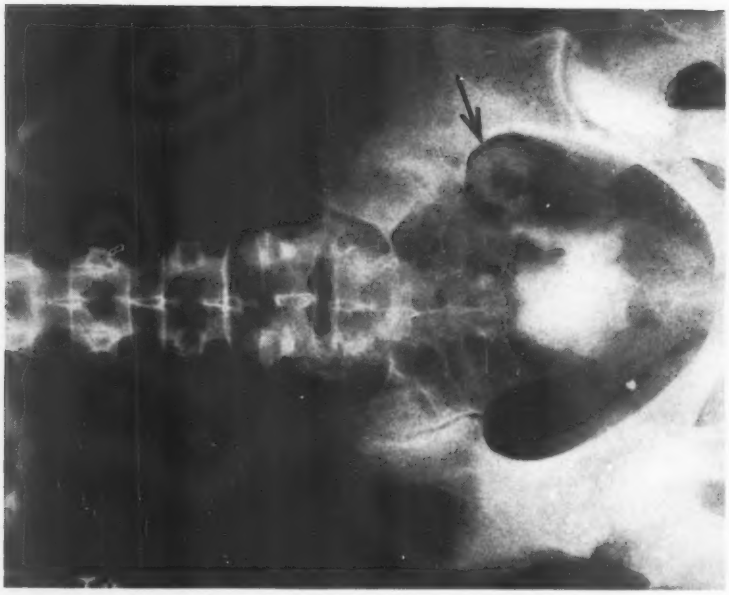


FIG. 11.—Case 5: Intravenous pyelogram, showing escape of dye through ureteral defect, into extraperitoneal abscess cavity.

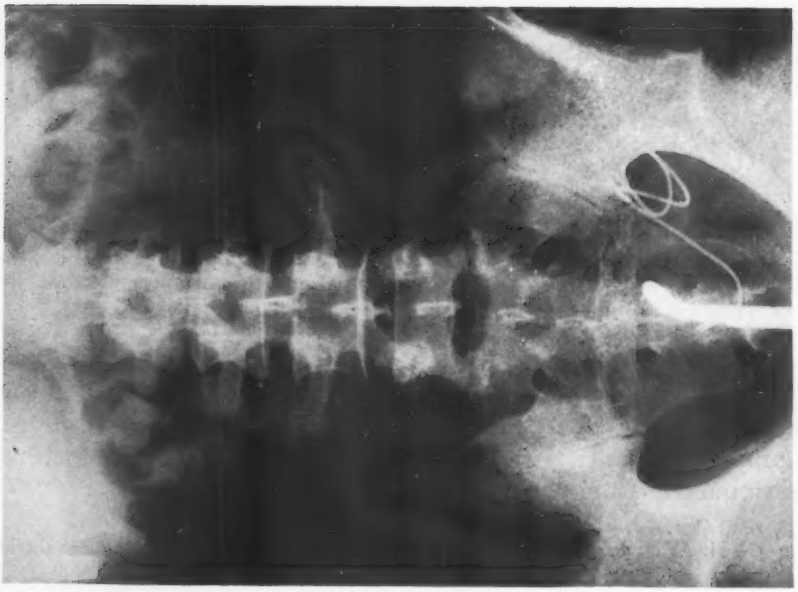


FIG. 10.—Case 5: Roentgenogram showing ureteral catheter escaping through defect in left ureter and coiling up in extraperitoneal abscess cavity.

sigmoid colostomy was done. The patient drained profusely both from the wound in the perineum and from the lower angle of the celiotomy incision. This drainage was not recognized as being urine.

The patient's postoperative course was somewhat stormy, but he was finally evacuated to the United States and admitted to Vaughan General Hospital on April 27, 1945. At admission, the abdominal wound was fully healed and the colostomy was functioning well. There was copious drainage of urine through the sinus in the buttock and the voided urine was grossly contaminated. Studies disclosed a large pelvic abscess filled with urine and cellular débris. No injury to the bladder was seen cystoscopically. An ureteral catheter introduced into the left ureteral orifice was found, roentgenologically, to be coiled in this abscess cavity. On May 10, 1945, the sinus track was opened widely and a No. 22 F. catheter introduced into the cavity from below, for free drainage. Gradually, the urine escaping through the perineal sinus decreased and finally stopped altogether. At this point the catheter was removed from the sinus. On July 7, the patient apparently developed a retroperitoneal mass which was thought to be a pelvic abscess. An attempt was made to incise and drain this through the perineum but was unsuccessful. Following this, after many unsuccessful attempts, an ureteral catheter was introduced into the pelvis of the left kidney. Pyelograms revealed only minimal back pressure on the left kidney but showed leakage of the dye in the region of the abscess cavity. It seemed apparent, therefore, that ultimate healing of the defect in the left ureter, in the presence of the residual abscess cavity, was not to be expected and that future stricture formation at this point would eventually destroy the left kidney. Consequently, on August 7, 1945, a left nephrectomy was performed.

Postoperative course was entirely without incident, and the perineal sinus track closed rapidly. Five weeks later, the sigmoid colostomy was closed, also without incident. The patient has remained well since (Figs. 10 and 11).

COMMENT: This case demonstrates the importance of early recognition of ureteral lesions. Had this patient had early adequate drainage, a secondary ureteral repair, or anastomosis into the bladder might have been done without the development of the large abscess cavity. With secondary infection, such a procedure was never possible. Further, the colostomy opening, situated as it was high in the left lower quadrant, greatly hindered surgical approach to either the left kidney or the left ureter.

SUMMARY

Due to the close association of viscera and organs of several systems within the pelvis, gunshot injuries of this region are among the most severe of war injuries. The pelvic fracture itself is relatively insignificant compared to the lethal potency of injuries to its contents.

The primary surgical management of these injuries, guided by the principles of prompt recognition; thorough repair; efficient diversion of urinary and fecal currents when necessary; and adequate drainage at all times, is of paramount importance, not only for the saving of life, but for the prevention and minimizing of distressing complications later.

Deviation from fundamental surgical principles in the early surgical care of gunshot injuries to the pelvis and its viscera results in increased mortality and morbidity, and in the necessity for further elaborate surgery, involving sacrifice of tissues and organs, with added risk to the patient.

Surgeons charged with the primary care of these injuries should be alert

to the possibilities of concealed extraperitoneal damage to the bladder, recto-sigmoid, and ureters. Injuries to the ureters are most often unrecognized at the time of primary operation when an unparalleled opportunity exists for the preservation of the associated kidney.

Proximal colostomies should divert and defunction, as well as decompress. Cecostomy is not an efficient diverting or defunctioning procedure.

The proper location of a proximal colostomy should take into consideration the likelihood of further reconstructive surgery upon the distal bowel. In wounds of the pelvic colon, especially, it may be wiser to place the colostomy no lower than the transverse colon, and to perform a complementary transverse colostomy along with exteriorization of a damaged pelvic colon.

Persistent fecal and urinary-fecal fistulae, particularly those traversing bone, require a direct attack for permanent closure, which is most satisfactorily done transperitoneally upon a bowel defunctioned by an efficient proximal colostomy. Following efficient fecal diversion, spontaneous closure of urinary-fecal communications often occurs provided urinary decompression or drainage is maintained, and urinary tract infection kept to a minimum. Reopening of such an apparently closed urinary-fecal communication commonly follows restoration of the fecal current indicating that direct attack on the fistula is necessary in the majority of cases for permanent cure.

The histories of five illustrative cases are presented.

BIBLIOGRAPHY

Coffey, R. C.: Remote or Indirect Subperitoneal Drainage in the Extraperitoneal Closure of Persistent Fecal Fistulae. ANNALS OF SURGERY, **45**, 827, 1907.

Colcock, B. P.: Traumatic Perforations of the Colon as Seen in a General Hospital. Surgery, **17**, 1, January, 1945.

Deaver, J. B.: The Traumatic Abdomen. ANNALS OF SURGERY, **68**, 275, 1918.

DeBakey, M. C., and Carter, B. N.: Current Considerations of War Surgery. ANNALS OF SURGERY, **121**, 545-563, May, 1945.

Dixon, C. F., and Deuterman, J. L.: The Management of External Intestinal Fistulas. J. A. M. A., **111**, 2095, 1938.

Dunn, J. S., and Drummond, H.: Ulceration of the Colon in the Neighborhood of Gunshot Wounds. Brit. Jour. Surg., **5**, 59-65, 1917-18.

Everidge, John: Injuries of the Ureter. Brit. Jour. Urol., **12**, 234, 1940.

Fullerton, Andrew: Observations on Bladder Injury in Warfare: A Study of 53 Cases. Brit. Jour. Surg., **5**, 248-288, 1917-18.

Gordon-Taylor, G.: Complicated Injuries of the Urinary Tract. Brit. Jour. Urol., **12**, 1-28, 1940.

Gordon-Taylor, G.: Second Thoughts on the Abdominal Surgery of "Total" War: A Review of over 1,300 Cases. Brit. Jour. Surg., **32**, 247-258, October, 1944.

Heyd, C. G.: The Increasing Usefulness of the Devine Colostomy in Left Colon and Rectal Surgery. ANNALS OF SURGERY, **116**, 913, 1942.

Lewis, D., and Penick, R. M.: Fecal Fistulae. International Clinics, Vol. I, Series 23, **111**, 1933.

Lichtman, A. L., and McDonald, J. R.: Fecal Fistula. Surg. Gynec. & Obst., **78**, 449, May, 1944.

Lockhart-Mummery, J. P.: Discussion on Methods of Making and Closing Colostomy Openings. Proc. Roy. Soc. Med., (London) **10**, 135, 1916-17.

Marshall, S. F., and Lahey, F. H.: The Surgical Treatment of Abdominal Fistulas. New Eng. Jour. Med., **218**, 211, 1938.

McCague, E. J., and Semans, J. H.: The Management of Traumatic Rupture of the Urethra and Bladder Complicating Fracture of the Pelvis. Jour. Urol., **52**, 36-41, 1944.

Morgan, C. N.; Wounds of the Colon. Brit. Jour. Surg., **32**, 337, 345, January, 1945.

Morgan, C. N.: Wounds of the Rectum. Surg. Gynec. & Obst., **81**, 56-62, July, 1945.

Neligan, G. E.: War Injuries to Genito-urinary Tract. Brit. Med. Jour., **2**, 291, 1939.

Ogilvie, W. H.: Abdominal Wounds in the Western Desert. Surg. Gynec. & Obst., **78**, 225, March, 1944.

Ogilvie, W. H.: Forward Surgery of Abdominal Wounds. Lancet, **246**, 555, 1944.

Poth, E. J., and Knotts, F. L.: The Clinical Use of Succinylsulfathiazole. Arch. Surg., **44**, 208, February, 1942.

Poth, E. J.: Succinylsulfathiazole and Phthalylsulfathiazole in Surgery of the Colon. Surgery, **17**, 773, June, 1945.

Reynolds, J. R.: War Injuries to the Genito-urinary Tract. Jour. Urol., **53**, 419-421, February, 1945.

Ross, J. C.: Injuries of the Urinary Bladder. Brit. Jour. Surg., **32**, 44-49, July, 1944.

Sandrey, J. G., and Mogg, R. A.: Wounds of the Bladder. Lancet, **1**, 716-720, June, 1944.

Senn, Nicholas: The Etiology, Pathology and Treatment of Intestinal Fistulae and Artificial Anus. Am. Jour. Obst., **3**, 321, 1894.

Uhle, C. A. W., and Erb, H. R.: Reconstruction of the Membranous Urethra. Jour. Urol., **52**, 42-59, 1944.

Wallace, Cuthbert: A Study of 1,200 Gunshot Wounds of the Abdomen. Brit. Jour. Surg., **4**, 679-778, 1916-17.

Wallace, Cuthbert: The Lettsomian Lectures on War Surgery of the Abdomen. Lancet, 1, 56, 596, 633, 1917.

Walter, C. F., Rollinson, H. D., Jordon, A. R., and Bank, A. G.: Five Hundred Emergency Operations for Abdominal Wounds. Lancet, 1, 207, 1917.

Young, H. H.: Wounds of Urogenital Tract in Modern Warfare. Jour. Urol., **47**, 59-108, 1942.

Dr. George B. Sanders
1417 Heyburn Bldg.
Louisville 2, Kentucky

STUDIES ON THE ACID DÉBRIDEMENT OF BURNS*

MARION B. SULZBERGER, M.D., ABRAM KANOF, M.D.,

AND

RUDOLF L. BAER, M.D.

NEW YORK, N. Y.

THERE IS GENERAL AGREEMENT that the early removal of the nonviable tissue or slough has a beneficial effect in most third-degree burns and in many other forms of necrotic wounds. It is also agreed that the optimum procedures for removal of nonviable tissue must be: (1) as gentle, nondamaging and "nonshocking" as possible; and (2) as "selective" as possible (*i.e.*, must remove the nonviable tissue and leave unharmed all the viable elements).

In recent years many investigators have devoted their efforts to the development of chemical methods which would remove slough more gently and more selectively than any available surgical or mechanical method. In 1940, Glasser[1] reported success in removing slough by the application of a proteolytic compound. Cooper, Hodge, and Beard[2] made a similar report in 1943, and Howes,[3] in the same year, suggested digestion of the slough by treatment with hydrochloric acid and pepsin. But these methods are generally rather slow, and the semidigested material offers a medium for bacterial growth. There is also reason to believe that these methods are not sufficiently selective and that some viable as well as nonviable tissue is proteolized, thus, helping to convert second-degree burns into third-degree lesions.

In 1944, Connor and Harvey[4] described a new method of slough removal. The authors reported that by their method, the slough was removed rapidly and selectively by the separation of large, membranous segments along a line of cleavage between the dead and the viable cells. The agent used by Connor and Harvey was *pyruvic acid in a water-starch gel* and their experimental work was done chiefly on dogs.†

---

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University Medical College.

We wish to express our gratitude to Dr. Milton C. Winternitz, Admirals Ross T. McIntire and Harold W. Smith and Dr. David P. Barr for their advice and cooperation.

The statements in this article are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

† Lam and Puppendahl working on experimental burns in dogs reported that cotton wet with distilled water was as effective in removing slough as pyruvic acid in starch paste (ANNALS OF SURGERY, 121, 866, June, 1945). It was not the purpose of our studies to compare the effects of wet compresses with other methods, as our objective was the development of an effective gel for field use. However, the data presented in the present report demonstrate that acid had a beneficial effect, as shown by the figures on comparative efficacy of "blank" starch paste *versus* the same paste containing pyruvic acid.

Because the Connor-Harvey method showed great promise, and because the topical treatment of burns formed a very substantial problem in war medicine, Division 5 and the Subcommittee on the Treatment of Infected Wounds and Burns of the Committee on Medical Research of the Office of Scientific Research and Development requested the present authors to undertake further studies of the new technic.

These studies had four major objectives:

(1) To compare the effect of the method developed by Connor and Harvey with the effect of other methods in the topical therapy of standard third-degree burns in human subjects.

(2) To elaborate a more practical vehicle to replace the starch paste gel, which is impractical, as it is unstable and must be freshly prepared each day.

(3) To find a more stable and more generally available acid to replace the pyruvic acid which is unstable and difficult to obtain in large quantities.

(4) To extend the sphere of knowledge regarding the technic, complications, advantages, disadvantages, and mechanisms of the new method.

The results of our experiments were reported in a series of 16 classified communications to the National Research Council. The wartime restrictions now being lifted, the purpose of the present report is to summarize our results and to present them in a form which will facilitate further trial of the method.

EXPERIMENTAL

Under authorization of the Secretary of the Navy, and other responsible authorities, the tests were performed on several hundred young male volunteers at the U. S. Naval Disciplinary Barracks at Hart's Island, New York.

Paired comparisons were used throughout. Two symmetrically situated areas, one on the flexor surface of each forearm, were burned in all subjects. The comparative efficacy of two treatment agents was then tested by applying the agent under study to one of these burns; and applying another agent, *i.e.*, the standard control material, in identical fashion to the sister burn on the opposite arm. The sites were then observed daily; and the day on which débridement took place, and later, the day of complete epithelization, was noted.

This method eliminates errors caused by the great differences in healing rate which occur in different individuals, in different skin areas, or which may be due to different diets and to many other factors. Moreover, it has been estimated (John Fertig, Columbia University, personal communication) that results based on healing rates obtained in a series of six men by this method, (where the effects of a new agent are estimated by comparison with the effects of a common standard control agent in the same individual) are often statistically as valid as results obtained by observing the healing rates of 50 burns treated with a new material without reference to the effects of a standard control treatment in the same individual.

In the earlier experiments, the burns were produced by the application of an accurately measured amount of liquid mustard gas. Previous experience with mustard gas had enabled us to develop a technic by which lesions of about

similar size and depth could be produced. These burns were approximately 4.0 cm. by 2.5 cm. in size. Excision and histologic examination of the burned areas showed that the lesions were largely third-degree burns, but with occasional islands of intact epithelial elements (usually pilosebaceous; at times sweat glands?) within the third-degree area.

Later experiments were conducted with thermal burns. These were produced with an apparatus designed and built by A. H. Moritz and F. C. Henriquez, of Harvard University. With this apparatus we applied to the skin a round copper disk 1.0 cm. in diameter at a temperature of 67° C. for 60 seconds. (The constant temperature was maintained by the apparatus in which the disk forms the bottom of a container in which methanol is *kept* boiling (temperature 67° C.) by passing an electric current through a high resistance wire in the walls of the container). No pressure was used except that exerted by the weight of the applicator itself. Histologic examinations showed that the resulting lesions were full-thickness third-degree burns with few glandular rests.

As a rule, the débriding applications were begun on the third, fourth or fifth day after the thermal burns, and on the seventh day after the mustard gas burn. This interval was allowed to elapse in order to permit some diminution of the early exudation. The medication was then applied in identical manner to all sites in all subjects. A tablespoonful (approx. 10.0 cc.) of the acid-containing agents or of the blank vehicle controls was applied to each lesion; the materials were immediately covered with a 2- x 2-inch square of gauze. This was covered with one or two layers of vaselined gauze to retard drying out. The vaselined gauze was, in turn, covered with dry gauze which was held in place by two wide strips of Elastoplast (Duke). This cover was made more air-tight by sealing the edges and seams with ordinary adhesive plaster. The agent was applied daily, the applications being continued until débridement took place in all the men of the series; or until further applications in a particular individual had to be stopped because of a prohibitive degree of irritation. On the average, débridement took a total of four to five days for a thermal burn; and eight to ten days for a chemical burn. When the débriding agent was discontinued, both lesions, with the exceptions noted in Table I, were treated identically. The postdébridement treatment was almost always a sulfonamide cream (5 per cent sulfadiazine, sodium sulfadiazine, sulfanilamide, or sulfathiazole), applied daily under a gauze dressing until epithelization was complete.

A. THE SEQUENCE OF EVENTS DURING ACID DÉBRIDEMENT

With the best agents, débridement of the thermal burns usually took place after the third or fourth application of the acid, *e.g.*, on the sixth to eighth day of the burn. In lesions which were about to débride, the slough turned yellowish-brown on the second day; a line of separation became visible at the periphery on the next day; and soon after the slough lay loose or almost loose, in the wound. These loose sloughs often came off "spontaneously" as the dressing was removed (Fig. 1), but more often they were held by a few

strands and were lifted off with a forceps (Fig. 2). With the slough off, a clean granulating base was generally disclosed.

It was observed early that the ulcer resulting from acid débridement of the slough was larger than an undébrided control lesion. This increase in size was especially noted when K-Y jelly was the vehicle for application of the acid. However, the scar which subsequently formed at the site of an acid-débrided burn, while slightly larger, was *smoother and more elastic* than that on undébrided lesions (Fig. 3).

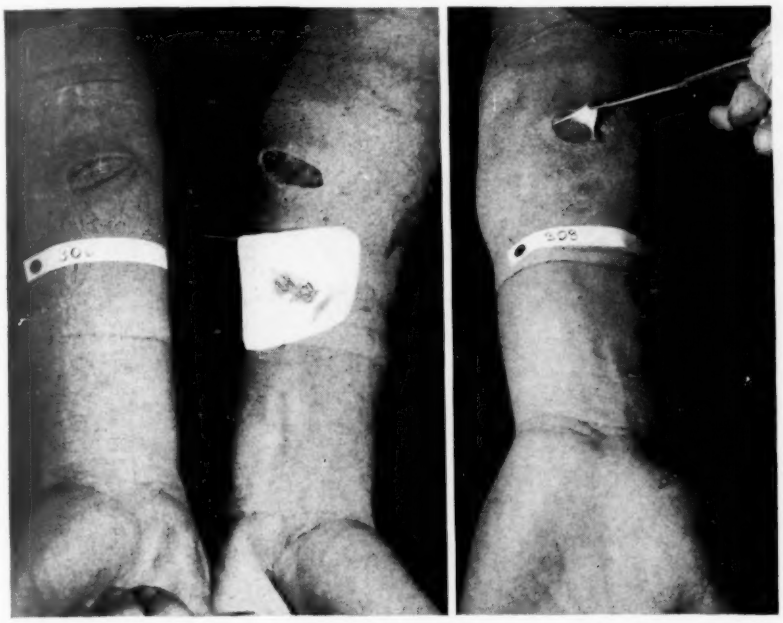


FIG. 1 FIG. 2

FIG. 1.—Successful removal of slough. Status at 13 days after application of mustard gas.

Right arm: Sodium sulfadiazine 5 per cent ointment applied at two days after contamination and reapplied daily.

Left arm: No treatment until 7th day; then pyruvic acid-starch paste applied daily for six days, at which time slough came off in one piece. (Slough shown lying on piece of gauze below ulcer on left arm.)

FIG. 2.—Chemical burn after seven applications of pyruvic acid in starch paste. The slough is ready to be lifted off as a membrane, revealing a clean base.

Another observation was the exceedingly small incidence of infection in these wounds. They were handled daily in an ordinary prison room, without the usual appurtenances or precautions for surgical sterility. Still, in over 1,500 lesions produced and treated, there was no serious or general infection, and only two or three arms developed a slight cellulitis and required hot soaks for a day or two. This is a far cry from the experience related by Lee and Rhoads[5] that they have never seen a third-degree burn treated with tannic acid which did not eventually develop an infection.

A follicular dermatitis of the surrounding normal skin, usually mild but *sometimes severe,* frequently followed the application of the acid. However, the dermatitis regularly cleared up within a few days after the discontinuance of the acid. It never seemed to interfere with healing except where the higher concentrations of acid, later to be discussed, were used.

FIG. 3.—Two equal chemical burns. The left arm was treated daily with sulfadiazine cream. The right arm was left untreated for seven days, then débrided with pyruvic acid in starch paste. At one month the right lesion is completely epithelized while the left still shows considerable slough.

B. COMPARISON BETWEEN HEALING TIME AFTER ACID DÉBRIDEMENT AND HEALING TIME WITH OTHER TREATMENT METHODS

In our first series of experiments, we were able to confirm the finding that application of 0.9 per cent (0.1 molar) pyruvic acid-starch paste* led to

* A 0.1 molar solution of pyruvic acid is prepared by adding 6.8 cc. pyruvic acid (Eastman No. 498) to one liter of distilled water (resulting p_H is 1.9). 80 grams of ordinary cornstarch are suspended in a few ounces of the cold pyruvic acid solution. The rest of the liter of 0.1 molar pyruvic acid is heated to the boiling point and the cold starch suspension is added slowly, with stirring. Heating is continued for a few more minutes and the resulting pyruvic acid-starch paste is allowed to cool. The p_H of the finished gel is 1.8 to 1.9.

débridement of thermal and chemical burns, as described by Connor and Harvey.[4] Moreover, application to a burn of 0.9 per cent (0.1 molar) pyruvic acid in starch paste daily until débridement took place and then daily dressings with 5 per cent sodium sulfadiazine cream resulted in quicker healing than could be achieved in a similar, symmetrically situated lesion treated as follows: (a) Left untreated; (b) treated daily with "blank" starch paste to which no acid had been added; (c) treated daily with pressure bandages with sodium sulfadiazine ointment; (d) treated daily with pressure bandages with sulfadiazine ointment; or (e) treated daily with pressure bandages with one-third per cent silver nitrate in petrolatum. The results of some typical experiments are shown in Table I. The indicated superiority of the acid débridement method was maintained throughout the entire series of over 1,500 wounds.

TABLE I

No. of Volunteers	Av. Heal. Time on 0.1 M. Pyr. Ac.-starch Paste and Later with Sod. Sulfadiaz. Cream, in Days	Agent Used on Symmetrical Lesion and Average Healing Time, in Days		Type of Burn
11	20.2	No treatment	30.9	Thermal
10	19.4	"Blank" starch paste	24.0	Thermal
13	30.0	"Blank" starch paste	39.7	Chemical
4	31.5	5% sod. sulfad. cream	42.8	Chemical
6	38.1	⅓% silver nitrate in petrolatum	49.8	Chemical
5	31.1	5% sulfad. cream	43.8	Chemical

C. COMPARISON OF PYRUVIC ACID WITH OTHER ACIDS

As soon as our results confirmed the value of acid débridement with pyruvic acid-starch paste, the next problem was to ascertain whether some other acid could be substituted for pyruvic acid. The question was of great practical importance, for pyruvic acid was difficult to obtain in sufficient quantity and was relatively unstable. The question also had its theoretic importance; while it seemed likely that the action of pyruvic acid might be an hydrogen ion effect which could be duplicated with other acids, the possibility had been suggested that the débridement might be due to properties peculiar to pyruvic acid. We, therefore, tested the action of the following other acids: hydrochloric, mandelic, tartaric, lactic, citric, and phosphoric acids.

Only one of the acids tested was found to be in all ways equal to pyruvic acid. This was phosphoric acid. In concentrations of 0.98 per cent (approximately 0.1 M.) phosphoric acid in starch paste at a p_H of 1.9 to 2.0 was found to débride chemical and thermal burns, and to accelerate their healing as efficiently as did pyruvic acid in starch paste.

Some of the other acids were approximately as effective as pyruvic if they were used in higher concentrations than 0.1 molar. Thus, 0.66 M. mandelic acid, 0.34 lactic acid, 0.2 tartaric acid, and 0.14 citric acid, all in starch paste, débrided the standard burn almost as quickly as did the 0.1 M, pyruvic acid in starch paste. However, the higher concentrations of acids in general produced a prohibitive degree of dermatitis of the surrounding skin. These same

acids in 0.1 M. concentration, *i.e.*, the concentration corresponding to that used with pyruvic acid and not producing excessive dermatitis, were relatively ineffective. Tartaric acid in this low concentration was an exception; at 0.1 M. strength, it was almost, but definitely not quite, as good as pyruvic acid.

Hydrochloric acid, because of its high degree of dissociation, produced a low initial p_H (about 1.9) when used at a concentration of 0.1 M., but was found to be ineffective in producing débridement. We believe that, as suggested by Connor and Harvey, this is due to lack of a reservoir of H. ions sufficient to maintain the low p_H for a long enough period of time.

Thus, our results completely confirm the findings of Harvey and Connor *that not only the original hydrogen ion concentration but the buffer capacity of the acid is important in the achievement of slough removal.* The more weakly dissociated acids have a larger reserve of hydrogen ions, and are able to maintain the low p_H for a longer period of time.

However, at the same molarity there appeared to be differences in the efficacy of different acids. Phosphoric acid 0.1 M. at a p_H of 1.9 was as good as pyruvic acid 0.1 M. at a p_H of 1.9; tartaric acid, 0.1 M. at a p_H of 2.0 and mandelic acid 0.1 M. at a p_H of 2.2 were not as good as pyruvic acid at a p_H of 1.9. Citric acid 0.1 M. at a p_H of 2.0 was inferior, while lactic acid 0.1 M., at a p_H of 2.3, was almost ineffective.

D. COMPARISON OF STARCH PASTE WITH OTHER VEHICLES

Starch paste in water, while an effective vehicle for acids, is a very impractical vehicle. A first drawback is due to the fact that the word "starch" does not designate a single, specific substance, but may refer to a number of powders produced by grinding various grains. Even starches from the same grain vary greatly from lot to lot. In the early experiments in which different brands of starch were used the different series of men frequently evidenced large differences in their rates of débriding and, therefore, in the healing time of lesions treated with pyruvic acid in starch paste. These variations were effectively reduced by buying a large quantity of different types of cornstarch and mixing the various lots to produce a pooled starch of uniform quality which could be used throughout.

But the principal impediment to the general usefulness of starch paste lies in the fact that the preparation of this paste is far too involved to be practical. The procedure is a form of cookery, necessitating not only dilution of the acid, but heating it, adding to it a small quantity of the starch powder and then mixing in the rest of the powder under constant stirring and heating. Moreover, the mixture must be prepared freshly each day. In order to eliminate these drawbacks a systematic series of experiments was begun in the attempt to discover a more suitable vehicle for the acid.

The essentials for a suitable vehicle were outlined as follows:

(1) It must be chemically compatible with the acids.

(2) It must facilitate free diffusion and delivery of the acid, for which reason there must be an aqueous outer phase.

(3) It must cause no irritation to the skin, either by itself or in combination with the acid.

(4) It must have no systemic toxicity as a result of absorption when used in the therapeutic quantities and concentrations.

(5) It must have a consistency suitable for application to all parts of the skin.

(6) (a) It must be capable of easy and rapid preparation. (b) It must be, with its contained acid, sufficiently stable and in other ways suitable for distribution and storage in practical packages.

The problem of finding such a vehicle was divided into two large subdivisions. The first was a search for a "ready made" gel vehicle in which the acid was present or could easily be added. The second was the elaboration of an hygroscopic powder containing the acid and other needed ingredients and which would produce a gel suitable for immediate use simply by the addition of water.

E. READY-MADE GELS

In the search for a "ready-made" gel, a total of 61 different formulae were prepared and tested.* On the basis of previous experience and preliminary tests, it was thought that there were two types of materials which could be omitted from further testing: (a) those which were highly irritating on skin test; and (b) those which showed poor diffusion of the acid in *"in vitro"* models.

As each of the 61 formulae could not be tested on actual burns without seriously depleting the supply of volunteers, a method of screening was elaborated by which the more promising formulae could be selected for further definitive testing. The screening skin tests were as follows:

(1) Each proposed material was used as a dressing on a group of normal arms and kept on for 24 hours. At the end of this time the skin was examined for evidence of irritation.

(2) At the same time, together with others, each material was placed as a patch test on the backs of another series of men.

Correlation of the results of these skin tests gave the relative irritancy of a series of materials; and indicated which were too irritating to warrant further trial.

The preparations which were not prohibitively irritating to the skin were then tested in the laboratory to screen for probable efficiency of action. Three types of laboratory tests† were employed to study the *in vitro* diffusion of acid out of vehicles:

---

* The following pharmaceutical houses participated in the development of these formulations: Bristol-Myers Co., Hillside, N. J., Arthur D. Little, Inc., Boston, Mass., and Norwich Pharmacal Co., Norwich, N. Y. Their coöperation in this work is gratefully acknowledged.

† Lt. George Rosenfeld, U. S. N. R., suggested and carried out these tests. We are grateful to him for his expert assistance which made this phase of our studies possible.

(1) Diffusion of the acid out of the vehicle into a colloidal aqueous gel containing alizarin as indicator. This turned from red to yellow, showing how far the acid had diffused in a given time (Fig. 4).

(2) Diffusion of acid out of the vehicle across a cellophane membrane into water, the p_H of which was regularly tested.

(3) Diffusion of an acid out of a vehicle directly into blood serum, the p_H of which was determined at intervals by submerging Beckman external titration electrodes in the serum layer without touching the vehicle.

These methods have been more fully described in a paper on methods.[6]

The acid-containing preparations which were found satisfactory by the above screening tests were then tested on chemical and thermal burns in human subjects.

RESULTS

As a result of all these tests, the following combinations were found to be equal to 0.1 M. pyruvic acid in starch paste in regard to such essential properties as effectiveness of slough removal, speed of healing produced, and low degree of irritancy:

1. Methyl cellulose—water gels with 0.1 M. pyruvic or phosphoric acid:		
(a)	Pyruvic acid	6.8 cc.
	Methyl cellulose (25 cps.)	170.0 Gm.
	Water	821.2 cc.
(b)	Phosphoric acid (85%—1.71 sp. gr.)	6.74 cc.
	Methyl cellulose (25 cps.)	170.0 Gm.
	Water	818.5 cc.
(c)	Pyruvic acid	6.8 cc.
	Methyl cellulose (4,000 cps.)	40.0 Gm.
	Sorbitol (Arlex)	10.0 Gm.
	Water	941.2 cc.
2. K-Y jelly with 0.4 M. pyruvic or phosphoric acid:		
(a)	Pyruvic acid	27.2 cc.
	K-Y jelly (Johnson & Johnson)	1,000.0 Gm.
(b)	Phosphoric acid	27.0 cc.
	K-Y jelly	1,000.0 Gm.
3. Pectin-Ringer's solution—glycerin gel with 0.1 M. pyruvic acid:		
	Pyruvic acid	6.8 cc.
	Pectin	30.0 Gm.
	Glycerin	79.3 cc.
	Ringer's solution	861.2 cc.

The more than 50 acid-containing preparations which were found to be unsatisfactory need not be listed here. But it may be stated that the unsatisfactory preparations included the following types of vehicles: silica gels, glycerin-starch pastes, methocel-petrolatum-water ointments, Tween-water emulsions, water-in-oil emulsions, vanishing cream-type emulsions and carbowax ointments.

F. POWDERS

In an effort to further simplify the use of the acid method for débridement, experiments were undertaken with dry, hygroscopic powders which contained both the acid and the elements of the vehicle and which needed only the

addition of water to complete the medication, forming gels ready for use in a few minutes. At our suggestion these combinations were developed by Drs. A. M. Mattocks and W. A. Lazier of the Southern Research Institute,[7] working under an O. S. R. D. contract on the "Treatment of Infected Wounds and Burns." We subjected the gels formed by these powders to the screening methods already described; and the more promising combinations were tested on third-degree burns in human volunteers by the paired comparison technic.

Seven formulae were found to be *almost* (but not quite) as effective as 0.1 M. pyruvic acid in starch paste with regard to both slough removal and shortening of healing time. They were all *better* than the pyruvic acid in starch as regards *lack of irritancy.*

The seven formulae are:

1.	Pyruvic acid	19. Gm.
	Methyl cellulose (4,000 cps.)	200.
	Xynomine	40.
	Mix two parts of the powder with 15 parts of water. *p*H of the gel is 1.87.	
2.	Pyruvic acid	66. Gm.
	Methyl cellulose	500.
	Mix 1 part of the powder with 13 parts of water. *p*H of gel is 2.0.	
3.	Pyruvic acid	36.8 Gm.
	Methyl cellulose	300.
	Sorbitol	60.
	Mix 1 part of the powder with 10 parts of water. *p*H of gel is 2.2.	
4.	Phosphoric acid	20. Gm.
	Methyl cellulose	300.
	Sorbitol	60.
	Mix 1 part of the powder with 10 parts of water. *p*H of gel is 20.0.	
5.	Pyruvic acid	26.6 Gm.
	Hydroxyethyl cellulose (WS-100)	300.
	Arlacel C	75.
	Mix 1 part of the powder with 3 parts of water. *p*H of gel is 2.24.	
6.	Pyruvic acid	17.8
	Hydroxyethyl cellulose (WS-500)	200.0
	Mix 1 part of the powder with 6 parts of water. *p*H of gel is 2.3.	
7.	Phosphoric acid	30. Gm.
	Methyl cellulose	300.
	Sorbitol	60.
	Mix 1 part of the powder with 10 parts of water. *p*H of gel is 1.79.	

DISCUSSION.—The technic of acid débridement seems to offer a safe, simple and practical method for the topical treatment of third-degree burns. In such experimental burns this treatment produces a clean, pink, granulating base suitable for skin grafting within three to five days after the beginning of treatment.[4] In the process, areas of viable tissue and areas of "second" and "first"-degree burn which are usually present in all severe cases, are saved to act as centers for reëpithelization. Quick removal of the dead tissue removes a good pabulum for bacterial growth and minimizes the absorption of toxic materials from destroyed tissue. Connor and Harvey[4] have suggested that in patients with large burns the acid treatment had best be started within two or three days, or as soon as peripheral vascular failure has been controlled. If the patient is first seen after the slough has been present for some time, acid

treatment is best begun immediately. The débriding material should be applied liberally over the burnt areas; for example, about 3,000 cc. for a burn involving the leg, or 6,000 to 8,000 cc. for a burn involving the entire thigh and leg. The adjoining unburnt skin may also be included in the dressing; an excess is safe, while insufficient amounts are ineffective. The medication should be covered with dry gauze, then with "vaselined" gauze, and the whole covered over by large sheets of gauze or linen. The burn is redressed every 24, 48 or 72 hours, depending on the amount of exudation and the rapidity of the drying out of the acid-containing preparation.

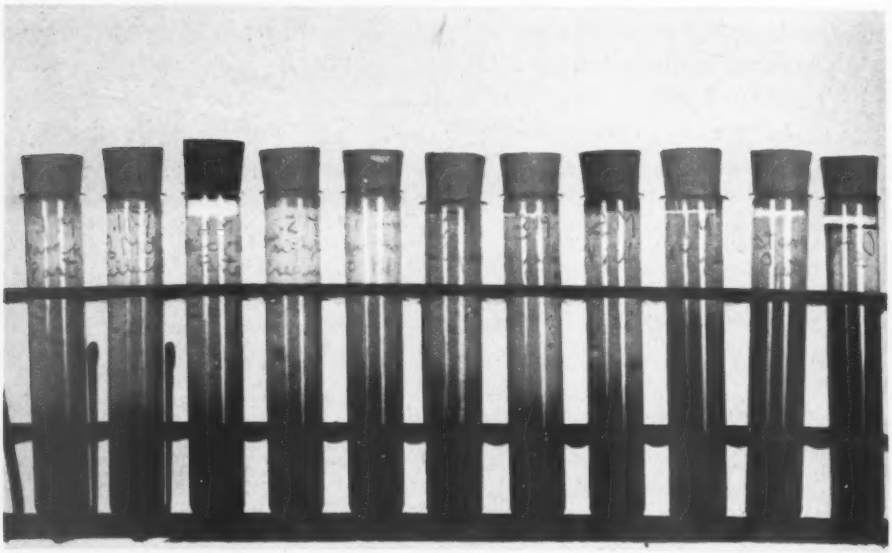


FIG. 4.—*In vitro* method of testing diffusion of acid through a medium (delivery from a vehicle). Each test tube contains the same amount of methyl cellulose and indicator solution. Above this have been layered different vehicles, each containing the same amount of acid. In the tube on the extreme left the acid has diffused about three-fifths of the way down. The tubes to the right of this show various degrees of diffusion; the two tubes on the extreme right are control tubes without acid. The third tube from the right shows complete lack of diffusion of the acid (from aquaphor).

The treatment would appear to be ideal for small burns where there is no question of shock or ultimate skin grafting. The total healing time is reduced by one-third to one-half, and the possibility of infection is almost entirely eliminated. A soft, pliant, scar is the end-result. The vehicles and acids already proved acceptable by our experiments are convenient enough for use under civilian conditions. The early perfection of the ready and stable powdered material should make use of the acid-débridement method even more acceptable. What is needed now to decide finally on the value of the method is a body of clinical experience.

SUMMARY

The method of débridement with 0.1 molar pyruvic acid in starch paste, first described by Connor and Harvey, was tested on a large group of male

human subjects. The tests were performed by comparing the pyruvic acid-starch paste method with other treatment methods on symmetrically situated small standard third-degree thermal and chemical burns on the flexor aspects of the forearm. (Method of paired comparisons)

The results showed that under the experimental conditions:

(1) Treatment with pyruvic acid-starch paste was more effective than treatment with "blank" starch paste in producing complete and rapid slough removal and, therefore, in accelerating healing.

(2) Treatment with pyruvic acid-starch paste and, subsequent to slough removal, with sodium sulfadiazine cream, produced more rapid healing than: (a) leaving the lesions untreated; or (b) treatment under pressure bandage with 5 per cent sodium sulfadiazine cream; or (c) with 5 per cent sulfadiazine cream; or (d) with ⅓ per cent silver nitrate in petrolatum.

We believe that our present results also support the concept that the effects of acid débridement are not specific for pyruvic acid. Acid débridement appears to be dependent on the maintenance of the correct supply of hydrogen ions over a sufficient period of time.

Among the other acids tested, 0.1 M. phosphoric acid, which has a p_H of 2.0 and which is a weakly dissociated acid, proved to be the best from all viewpoints. It was approximately as effective in slough removal and in accelerating healing as was 0.1 M. pyruvic acid.

After lengthy studies it was found possible to replace the impractical starch paste vehicle previously used for acid débridement by several other vehicles.

The following formulae were as effective as 0.1 M. pyruvic acid in starch paste vehicle in producing slough removal and in accelerating healing of chemical and thermal burns:

0.1 M. pyruvic acid in methyl cellulose—water gel.
0.1 M. phosphoric acid in methyl cellulose—water gel.
0.1 M. pyruvic acid in methyl cellulose—Sorbitol—water gel.
0.4 M. pyruvic acid in K-Y jelly.
0.4 M. phosphoric acid in K-Y jelly.
0.1 M. pyruvic acid in pectin-glycerin-Ringer's solution gel.

Our final studies, together with Mattocks and Lazier, demonstrated that certain forms of dry hygroscopic powders containing the acids could be prepared. These, on addition of the proper amounts of water, rapidly formed suitable gels. Seven formulae of powders are submitted; these on the addition of water almost immediately formed gels which were shown to be less irritating and almost as effective as pyruvic acid-starch paste in removing slough and promoting healing of chemical and thermal burns.

REFERENCES

[1] Glasser, S. T.: A New Treatment for Sloughing Wounds. Am. J. Surg., **50**, 32–322, 1940.

[2] Cooper, G. R., Hodge, G. B., and Beard, J. W.: Enzymatic Débridement in the Local Treatment of Burns. Am. J. Dis. Child., **65**, 909–911, 1943.

[3] Howes, E. L.: Progress Report No. 9 Committee on Medical Research of the Office of Scientific Research and Development.

[4] Connor, G., and Harvey, S. C.: The Healing of Deep Thermal Burns. ANNALS OF SURGERY, **120**, 362–366, 1944; and personal communication.

[5] Lee, W. E., and Rhoads, J. E.: Present Status of Tannic Acid Method in Treatment of Burns, J. A. M. A., **125**, 610–612, July 1, 1944.

[6] Sulzberger, M. B., Baer, R. L., Kanof, A., and Lowenberg, C.: Methods for the Rapid Evaluation of the Beneficial and Harmful Effects of Agents Applied to the Human Skin. J. Invest. Dermat. **7**, 227–238, (Oct.) 1946.

[7] Mattocks, A. M., and Lazier, W. A.: Hydrophilic Acid Ointments for the Débridement of Burns. J. Amer. Pharmac. Assoc., Scientific Edition, **35**, 275–279, 1946.

EXTREMITY REFRIGERATION WITHOUT TOURNIQUET LIGATION IN CASES OF ACUTE ARTERIAL DEFICIT*

LT. (jg) KENNETH E. LIVINGSTON, M.C.,(S), U. S. N. R.

BOSTON, MASSACHUSETTS

FROM THE PERIPHERAL NERVE CENTER, U. S. NAVAL HOSPITAL, OAKLAND, CALIFORNIA.

EXPERIMENTAL STUDIES by Frederick Allen,[1, 2] in 1938 and 1939, demonstrated that intact limbs can survive complete ischemia for significant periods if adequately cooled. In 1941,[3, 4] these observations were applied clinically to amputation under tourniquet ligation and refrigeration. There is now considerable clinical experience[5-9] to show that this method has real value in preparing for and reducing the risk of amputation in the presence of advancing gangrene and toxic absorption, or in cases of massive trauma to the limb. Absorption from the damaged tissues is terminated by the tourniquet, pain is rapidly alleviated by the cooling, and physiologic amputation is accomplished in the sense that the limb is isolated from the circulation. Anatomic amputation can then be undertaken at reduced risk, and in most instances without supplemental anesthesia.

Limbs which are subsequently to be amputated are ligated by tourniquet and cooled to levels usually 2°–8°C. above freezing. Under these conditions, it has been shown that changes which are probably irreversible occur in the tissues. The tissue changes are a combined result of cooling and of the complete ischemia produced by the tourniquet. On the basis of present clinical experience, tourniquet ligation and refrigeration are appropriate only as preparation for amputation, and cannot safely be employed when survival of the limb is anticipated. However, clinical and experimental studies have not adequately differentiated between pathologic change due to cooling and that secondary to prolonged total ischemia. There is evidence both from clinical and experimental studies that the more severe changes may be attributable to tourniquet ischemia rather than to cooling. It is, therefore, possible that refrigeration *without* tourniquet might be successfully employed in some cases of acute vascular deficit in which survival of the limb is anticipated.

In experimental animals, Bruneau and Heinbecker[10] have found clinical and microscopic evidence of nerve injury after prolonged tourniquet ligation and cooling, but express the opinion that "although direct injury from cold may play a minor rôle, the degenerative changes are regarded as being due essentially to ischemia of the part during and following the cooling period." Evidence that these changes are reversible is apparent in the clinical recovery of the animals, and in the microscopic evidence of reparative processes in the injured nerves. Denny-Brown[11] has shown that although loss of myelin and degeneration occur following prolonged cooling, regeneration is rapid and com-

* The opinions expressed in this article are the private views of the author and are not to be construed as official or reflecting the views of the Navy Department.

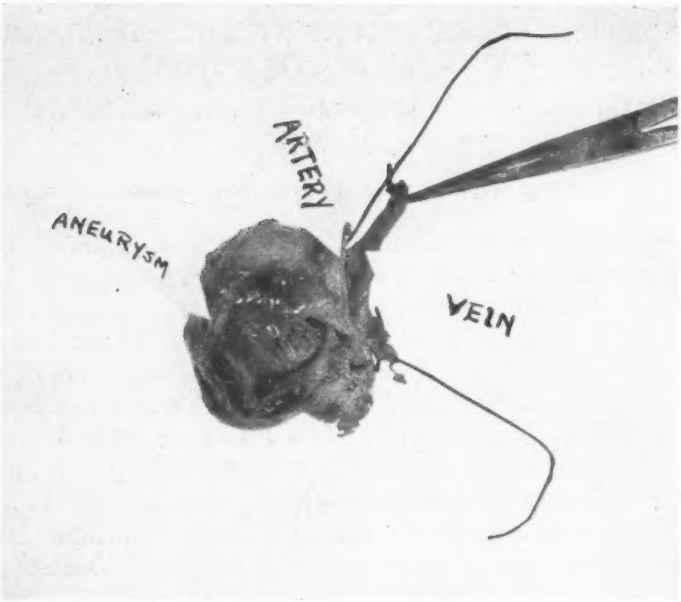


FIG. 1.—Popliteal Aneurysm. The ligature was threaded through the artery to show the opening into the aneurysm. The most recent clot had been removed to show the older thrombus and remaining cavity. There was no arteriovenous communication.

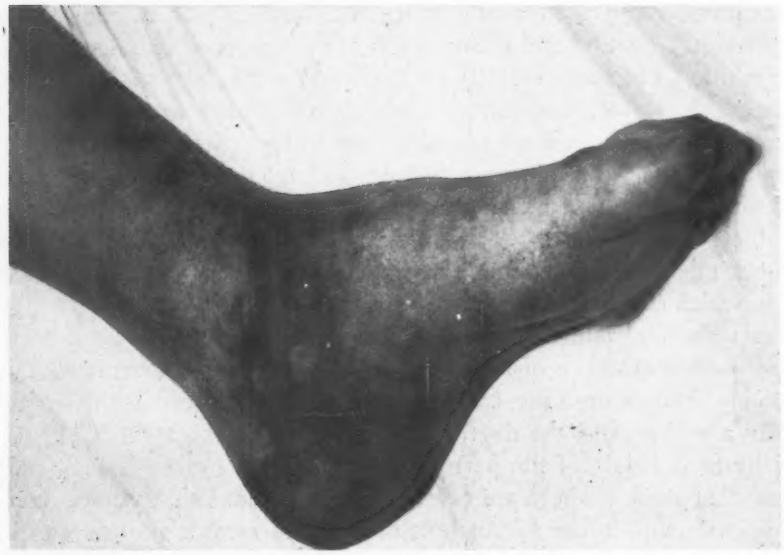


FIG. 2.—Appearance of the foot after four days of cooling. The entire foot was grayish in color, with a dark bluish band about the ankle and heel. This area looked prenecrotic. There was early drying of the tips of the toes.

plete in all grades of injury short of complete necrosis (produced by hard freezing with carbon dioxide snow).

There are a few clinical reports of refrigeration without the use of tourniquet. In 1944, Ottaway and Foot[12] reported a case in which prolonged refrigeration without tourniquet was used in attempt to preserve an extremity damaged by extensive shell fragment wounds severing the femoral artery and vein. This leg was cooled for one week from 2°–4°C., and then brought slowly up to 14°–16°C. Amputation just above the knee was performed after 29 days of refrigeration. Unfortunately, no pathologic study could be made in this case. Cayford and Pretty,[13] in 1945, reported a series of 18 amputations under refrigeration in which no tourniquet was used. No pathologic study of the cooled tissues was presented. Richards,[14] in 1944, reported a case in which refrigeration was carried out for a period of 19 days without tourniquet, in an attempt to save a limb following femoral and popliteal embolism. Pathologic studies in this case are of great interest. Muscle showed marked degenerative change "with only sarcolemmal nuclei remaining," the skin showed some epidermal necrosis, and there were "mild degenerative changes" in the nerves. The distal circulation of the leg and foot was remarkably preserved, as shown microscopically and by injection of the vessels. However, conclusions based on this study regarding the value of refrigeration in attempts to save an ischemic extremity were pessimistic. Further clinical experience would be valuable in confirming or modifying these views.

FIG. 3.—Appearance of the foot after 15 days of cooling. The area of marked discoloration about the ankle and heel had cleared, although the upper margin is still discernible. Erythema later developed along this line and finally a fine margin of superficial blistering. The skin and subcutaneous tissues of the weight-bearing areas showed further return toward normal, which persisted until the time of amputation.

We have recently used refrigeration without tourniquet over a period of 30 days in an attempt to save a lower extremity following acute occlusion of the popliteal artery and its major branches. Tissue studies following amputation were of sufficient interest to warrant reporting the case:

Case Report.—This 20-year-old enlisted man was wounded on Okinawa, April 6, 1945, during an enemy strafing attack. He sustained a small shrapnel wound in the left popliteal space at the level of the head of the fibula, with complete loss of peroneal nerve function. Two days after wounding it was noted in his health record that he had "two-plus" edema of the left foot and that "pedal pulses were barely palpable."

He was admitted to this hospital May 23, 1945, six weeks after wounding. Examination showed complete peroneal nerve paralysis with a palpable sensitive proximal neuroma beneath the healed popliteal wound. The foot was hyperesthetic and painful; the leg was

held flexed on the thigh; the foot was dusky and cool and with very poor pulses and slow venous filling after elevation blanching. Beneath the entry wound there was a rounded, walnut-sized pulsating mass with a loud systolic murmur and palpable thrill. With proximal obliteration of the artery there was occasional slowing of the pulse, but no increase in blood pressure. Pedal pulses disappeared completely with compression of the artery proximal to the lesion.

He was placed on a program of intermittent and increasing periods of proximal compression. There was some evidence that his collateral circulation was improving, but, June 18, 1945, there was a sudden arterial occlusion during rest. The foot blanched rapidly and became completely white, the popliteal thrill and pulse disappeared objectively and subjectively, and the foot became rapidly numb and then painful. Within less than one hour from the onset of symptoms he was given spinal anesthesia with a cutaneous level to the xiphoid. There was no change in the color of the foot and no return of pulse. Operation followed immediately, hoping that it would be possible to remove a thrombus from the artery. At operation, there was a large aneurysmal sac (Fig. 1) without associated arterial or venous dilatation. The sac was filled with recent thrombus. The bifurcation of the popliteal was exposed and the artery opened just proximal to this level. There was no clot in either anterior or posterior tibial arteries, but almost no back-bleeding. Quadruple ligation and excision of the shortest possible segment of artery and vein was then carried out. Immediately following operation the foot was unchanged and appeared cadaveric.

It was felt that amputation was inescapable. Refrigeration was undertaken in the hope that if gangrene could be postponed, the collateral bed might be opened sufficiently to allow survival of the foot or permit a more limited amputation (Fig. 2).

It was planned to cool only the distal tissues in which the most severe vascular deficiency existed, in order to avoid setting up spasm of collateral vessels in the calf. It was also planned to cool only to levels that would permit tissue survival and to raise the temperature as rapidly as tolerated. Cooling was started within four hours of the first symptoms of occlusion. Ice bags were used, covering only the foot to the level of the malleoli.

During the first 24 hours the temperature between the toes averaged 16.4°C. It was lowered to 14.3°C. during the next 24 hours, and from that time until cooling was terminated, the temperature ranged between 13.5° to 16.5°C. (56.3° to 61.7°F.) On two occasions on the second and third days the temperature of the foot rose to 20°C., and in each instance the appearance of the foot definitely changed, cyanosis became more marked and spontaneous pain appeared.

There was little or no pain in the foot while cooling was maintained but there was pain for a period of 10–12 days in the calf. During this period there was marked swelling, amounting to nearly two inches of calf circumference, sufficient to make the skin tight and shiny. This was serious, because we felt that much of his collateral circulation was in the superficial tissues and was probably obstructed by this edema. The edema did not involve the foot, and was undoubtedly due to necrosis occurring in the calf muscle mass. Evidence of this necrosis was still apparent at the time of amputation one month later.

In an attempt to open collateral four spinal anesthetics were given without evident change in the condition of the foot. He received nitroglycerin, in 1/100 gr. doses, followed later by ertyryltetranitrate and intravenous papaverine. It was possible that these medications were helpful, but not to a striking degree.

During the first 10 days it was felt by all observers that amputation was inevitable, but as edema of the calf subsided the foot showed definite improvement. Large areas of blotchy venous stasis which had earlier appeared irreversible cleared completely (Fig. 3). The deep tissues in the weight-bearing areas remained pliable, and skin condition remained excellent until the end of the fourth week. During the fourth week a line of blotchy erythema developed just above the ankle, proximal to the level of cooling. Cooling was then extended proximally to include this area, and during the last few days no attempt

FIG. 4.—Dorsalis pedis artery, showing the organized thrombus with recanalization of the main vessel. There is a small, old, organized mural thrombosis in the vessel at the right. Other vessels were patent and contained intact cells.

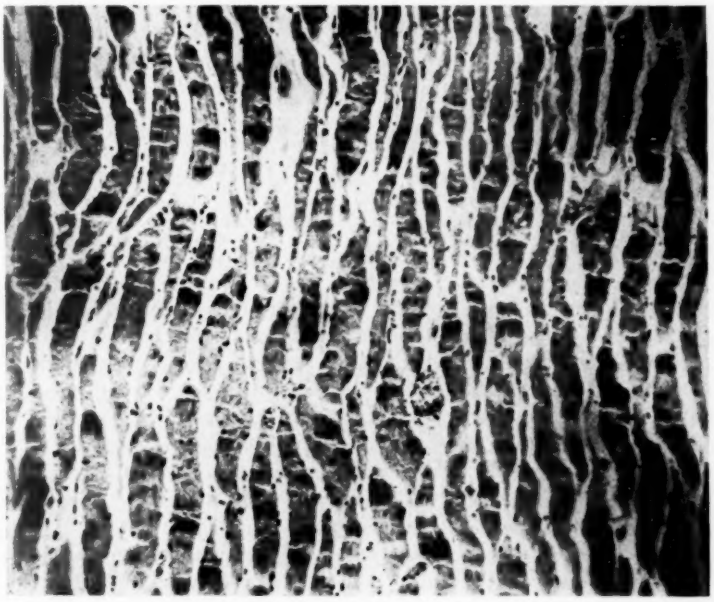


FIG. 5.—Deep plantar muscle (flexor digitorum communis). There is no evidence of necrosis or degenerative change in the muscle tissue and no cellular infiltration.

was made to refrigerate the distal portion of the foot. The distal portions of all toes demarcated with dry necrosis. On the 25th day a small line of superficial blistering appeared at the margin of the erythema above the ankle. The remaining areas of the foot looked good, but because this margin of blister persisted he was transferred on the 28th day to an Amputation Center for study. During the following 48 hours cooling was discontinued, and the foot showed considerable deterioration. A marked edema spread over the dorsum of the foot, and superficial blistering developed in this area. On the 30th day amputation was performed six inches below the knee. There was still extensive grayish

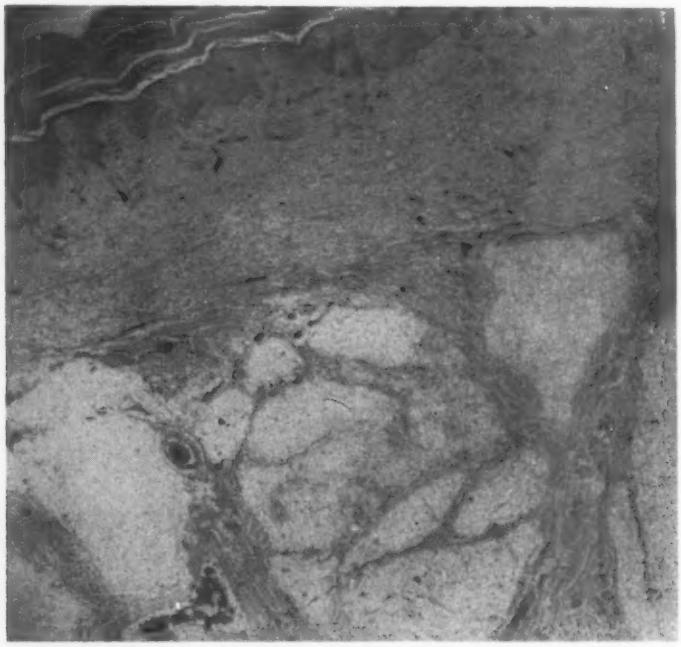


FIG. 6.—Skin, subcutaneous tissue and fat from plantar surface of the heel. Vessels in all layers appear widely patent and contain intact cells. All weight-bearing areas showed similar microscopic findings.

necrosis of the calf muscle mass and the wound was not closed primarily. Secondary closure later was uncomplicated and the stump was satisfactory.

Pathologic Examination.—Gross: Dissection and tissue fixation was done within four hours. Grossly, neither of the major vessels was patent or could be injected for radiopaque roentgenologic studies. Except for the subcutaneous edema over the dorsum of the foot and the superficial blistering in this area, all subcutaneous and deep tissues in the foot looked normal. The skin of all weight-bearing areas was entirely intact, subcutaneous fat was of normal consistency, and muscle tissue appeared normal. *Microscopically*, there was an old organized thrombus in the entire length of the anterior tibial and dorsalis pedis arteries (Fig. 4). These vessels had been extensively recanalized, and the thrombus was well-organized, indicating that it had occurred initially or very soon following the vascular accident. The thrombus in the distal posterior tibial artery was very recent, and probably occurred within the 48-hour period preceding amputation. Beneath one area of marked marginal erythema and blistering above the ankle a microscopic venous thrombosis was found. This occurred in a subcutaneous vein close to denuded skin. The thrombosis contained a large number of polymorphonuclear cells, and was surrounded by a small zone

of perivascular infiltration. This was the only evidence of infection noted in any of the tissues. The process was acute and probably started within the period after cooling was discontinued. No other gross or microscopic thromboses were demonstrable. The distal branches of the peroneal and tibial nerves showed mild degenerative changes.

COMMENT.—In retrospect, we would make certain changes in the management of such a case. First, we would cool the entire limb from the knee distally, in the hope that this would prevent or reduce the marked edema that developed in the calf muscles. It is our opinion that this period of edema interrupted considerable circulation to the distal limb, and was a serious complication. Secondly, we would suggest alcohol block or lumbar sympathetic ganglionectomy on the affected side. Although there was no definite evidence from spinal anesthetics that vasospasm was a significant factor in this case, sympathetic interruption would have assured maximal delivery of blood to the deficient area.

SUMMARY

Following an acute and severe vascular accident secondary to traumatic aneurysm of the popliteal artery, cooling of the distal extremity was carried out for a period of 28 days prior to amputation. During the interval of observation, changes which were assumed by all observers to have been irreversible regressed, and the appearance of the foot strikingly improved. Following amputation there was gross and microscopic evidence that revascularization was taking place in the cooled tissues and that the nutrition of the deep muscle tissues and weight-bearing skin and subcutaneous tissue of the foot had been well-maintained. These studies did not indicate that the smaller circulation in the cooled areas had been extensively shut down by vasoconstriction due to cold. On the contrary, we were impressed by the wealth of small patent vessels in all tissues and also by the active recanalization processes in the thrombosed segments of major arteries.

BIBLIOGRAPHY

[1] Allen, F. M.: Surgical Considerations of Temperature in Ligated Limbs. Am. J. Surg., **45**, 459–465, 1939.

[2] Allen, F. M.: Experiments Concerning the Ligation and Refrigeration: With Respect to Local Intoxication and Infection. Surg., Gynec. and Obst., **68**, 1047–1051, 1939.

[3] Allen, F. M.: Reduced Temperatures in Surgery. Am. J. Surg., **52**, 225–237, 1941.

[4] Crossman, L. W., Ruggiero, W., Hurley, V., and Allen, F. M.: Reduced Temperatures in Surgery. Arch. of Surg., **44**, 139–156, 1942.

[5] Perlow, S.: Refrigeration Anesthesia in Leg Amputation. U. S. Naval Med. Bull., **42**, 433–437, February, 1944.

[6] Hinchey, P. R.: Refrigeration in Surgery of the Extremities. N. E. J. M., **230**, 63–69, January 20, 1944.

[7] O'Neil, E. E.: The Use of Refrigeration in Amputations and Peripheral Vascular Disease. N. E. J. M., **230**, 209–216, February 24, 1944.

[8] McElvenny, R. T.: Refrigeration in Trauma of the Extremities. Surg. Clin. of N. America, **25**, 192–209, February, 1945.

[9] Mock, H. E.: Refrigeration in Trauma: Clinical Report. Am. J. Surg., **67**, 424–435, February, 1945.

[10] Large, A., and Heinbecker, P.: Nerve Degeneration following Prolonged Cooling of Extremities. ANNALS OF SURGERY, **120**. 742–749, November, 1944.

[11] Denny-Brown, D.; Adams, Raymond D.; Brenner, Charles, and Doherty, Margaret M.: The Pathology of Injury to Nerve Induced by Cold. J. Neuropath. & Exp. Neurol., **4**, 305–323, October, 1945.

[12] Ottaway, J. P., and Foote, J. J.: Refrigeration of Wounded Extremities. U. S. Naval Med. Bull., **43**, 1041–1043, November, 1944.

[13] Cayford, E. H., and Pretty, G.: Refrigeration Anesthesia and Evaluation of Amputation Sites by Artenogram. ANNALS OF SURGERY, **121**, 157–163, February, 1945.

[14] Richards, V.: Refrigeration Anesthesia in Surgery. ANNALS OF SURGERY, **119**, 178–200, February, 1944.

PRIMARY FIBROSARCOMA OF THE LIVER*

THOMAS A. SHALLOW, M.D., AND FREDERICK B. WAGNER, JR., M.D.

PHILADELPHIA, PA.

FROM THE SAMUEL D. GROSS SURGICAL DIVISION OF THE JEFFERSON MEDICAL COLLEGE HOSPITAL

THE ABDOMINAL SURGEON may at any time be confronted with a primary hepatic tumor requiring resection. Numerous reports, dating back many years, have proven the feasibility of this seemingly formidable procedure. Cures for as long as seven years following removal of malignant tumors[1] have dispelled doubt as to its value. So few cases are encountered by the individual surgeon, however, that his knowledge of the most suitable methods of excision for particular types is dependent upon the isolated experience of others. It is the purpose of this paper to add an unusual case of primary fibrosarcoma of the liver and to review the accepted methods of resection.

Case Report.—A. V., a white male, age 60, was admitted as a private patient to the Jefferson Medical College Hospital, November 18, 1945, with the chief complaint of abdominal enlargement.

The patient was well until July, 1945, at which time he began to experience a persistent bitter taste in his mouth. In August he observed an enlargement of his abdomen. At this time he began to lose his appetite. After eating only a small fraction of his normal meal, he would feel distended and extremely uncomfortable. During the ensuing three and one-half months before admission the abdominal enlargement gradually increased, he lost 40 pounds in weight, and grew progressively weaker.

The past medical and family histories were not significant.

Physical Examination.—The patient was a somewhat emaciated elderly male who appeared chronically ill. There was slight paleness of the mucous membranes but no evidence of jaundice. The temperature was 99.4° F.; pulse 100; respirations 24; and blood pressure 150/90. The significant findings locally were confined to the abdomen. On inspection, there was a dome-shaped enlargement resembling that seen in pregnancy at full term, the greatest prominence, however, appearing to be upper abdominal. Palpation revealed a round, firm, smooth, nontender mass about ten inches in diameter, fixed in the upper abdomen but somewhat movable below. It descended with respiration and was dull to percussion. A fluid wave could not be elicited.

Laboratory Studies.—The hemoglobin was 68 per cent; red blood cells 3,400,000, and white blood cells 8,500 per cu. mm., the differential count revealing 73 per cent neutrophils (3 per cent young forms), 21 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophils. Routine urinalyses and Fishberg concentration test were normal. A plain roentgenogram of the chest was negative. Roentgenologic study of the gastro-intestinal tract with barium revealed upward and backward displacement of the stomach and small bowel by a soft-tissue mass lying anteriorly. The six-hour film showed the stomach and small bowel still displaced in ringlet-formation around the mass (Fig. 1a). The colon was displaced anteriorily and to the periphery of the mass (Fig. 1b). There was no evidence of peptic ulcer or intrinsic gastro-intestinal neoplasm. These findings were interpreted as probably due to an omental cyst.

Preoperative Course.—A high caloric, high protein, high carbohydrate, low fat diet, and large doses of vitamin K were administered. During the eight days prior to operation

* Read before the Philadelphia Academy of Surgery, April 8, 1946.

the temperature fluctuated between normal and 100° F., and the pulse between 80 and 100. *Preoperative Diagnosis:* Possible omental or mesenteric tumor.

Operation.—November 26, 1945: Under pontocaine spinal anesthesia, a right rectus muscle-splitting incision was made over the summit of the mass and the peritoneal cavity entered. No free fluid was encountered. A firm, highly vascular, peritonized tumor was exposed, replacing most of the left lobe of the liver and extending downward to the level of the iliac crests. It was slightly adherent by fine adhesions to the surrounding coils of bowel.

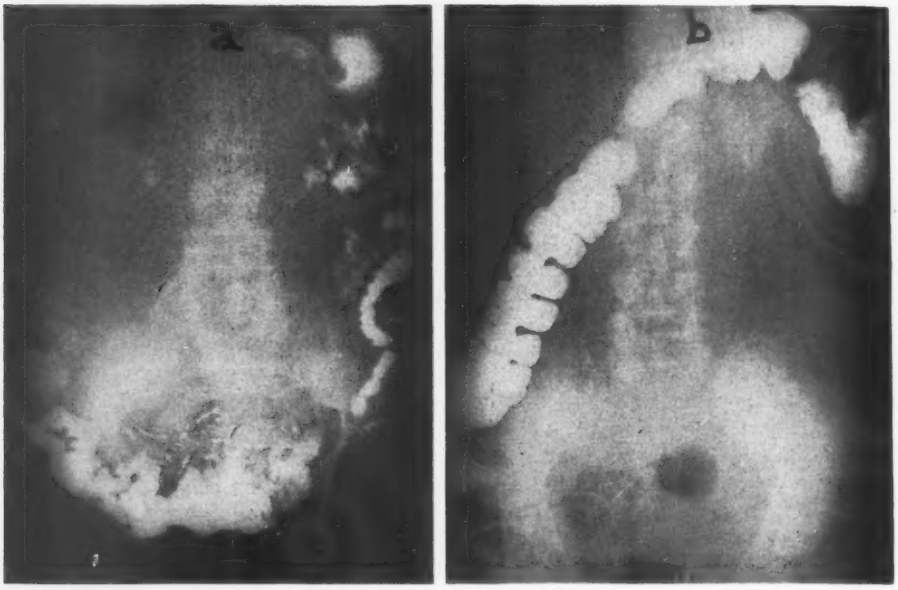


FIG. 1.—Gastro-intestinal series, showing stomach and small bowel in (a) and colon in (b) displaced in ringlet-formation around the mass.

An attempt was made to free the mass from the under surface of the liver, but considerable hemorrhage was encountered, and this method of approach had to be abandoned. The mass itself as well as the left lobe and part of the right lobe of the liver were then delivered into the incision. It was now found that the blood supply to the tumor could be controlled by an approach from its posterior aspect. Numerous large vessels, many the size of the radial artery, were encountered. Each was divided as it was exposed. When about half of the tumor was freed by this method, the entire tumor and remainder of the left lobe could then be delivered easily and completely into the incision. The remainder of the blood supply to the tumor was exposed and clamped as the tumor and immediately adjacent portion of left lobe were removed. Part of the round ligament was involved by the tumor and was included in its removal.

At the completion of resection, about one-third of the left lobe remained, and was a thin shell which oozed blood and bile. Suture ligatures were applied to the large vessels controlled by the clamps. The oozing was controlled by approximating the two raw areas of the under surface of the liver with interrupted mattress sutures of No. 2 chromic catgut. An iodoform gauze pack was placed against the sutured liver bed and a Penrose drain adjacent to the foramen of Winslow. The wound was then closed in layers around the drains.

The patient received 500 cc. of whole citrated blood during the operation, which lasted 55 minutes, and he remained in good condition.

Pathologic Examination.—Gross: The specimen consists of a peritonized nodular mass of tissue weighing 5,200 Gm. (Fig. 2). On cut-section there are a few large necrotic areas, but for the most part the tissue is firm and smooth (Fig. 3).

Histologic Examination.—The section consists of tissue from a tumor attached to the liver. It is made up at the periphery of bundles of fibrous tissue that, in general, do not show much change (Fig. 4). Sections taken from the central portion of the tumor,

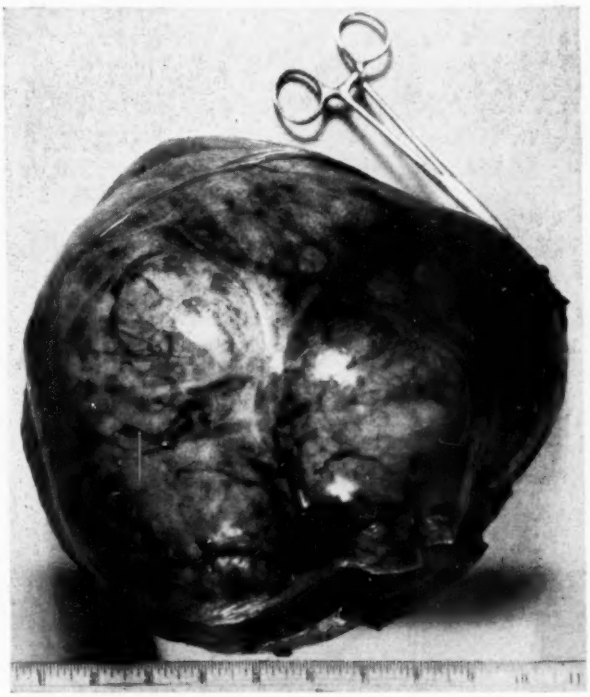


FIG. 2.—Gross specimen of fibrosarcoma, with hemostat on involved portion of round ligament.

however, are very cellular and show very definite sarcomatous change (Fig. 5). There are many large giant cells and many cells with multiple nuclei. Throughout the tumor there is extensive necrosis. *Pathologic Diagnosis:* Fibrosarcoma of the liver.

Postoperative Course.—The immediate postoperative response and early convalescence were uneventful. Small quantities of bile drained from the wound for three days. The drains were gradually withdrawn between the 7th and 10th postoperative days, during which time the patient tolerated a full house diet and was apparently doing well. The vital readings remained essentially normal after the 4th postoperative day. On the morning of the 11th day he got out of bed unaided and collapsed. In spite of artificial respiration and administration of cardiorespiratory stimulants, the patient promptly expired. Permission for postmortem examination could not be obtained. The cause of death was thought most probably due to embolism.

DISCUSSION.—The vast majority of primary hepatic tumors are epithelial, originating in liver cells (benign and malignant hepatomas) or in bile ducts (benign and malignant cholangiomas). Carcinoma of the liver cells is the most common. Warvi[2] collected 1,200 histologically-studied cases up to 1944. The

FIG. 3.—Cut-section of tumor, showing central sarcomatous area.

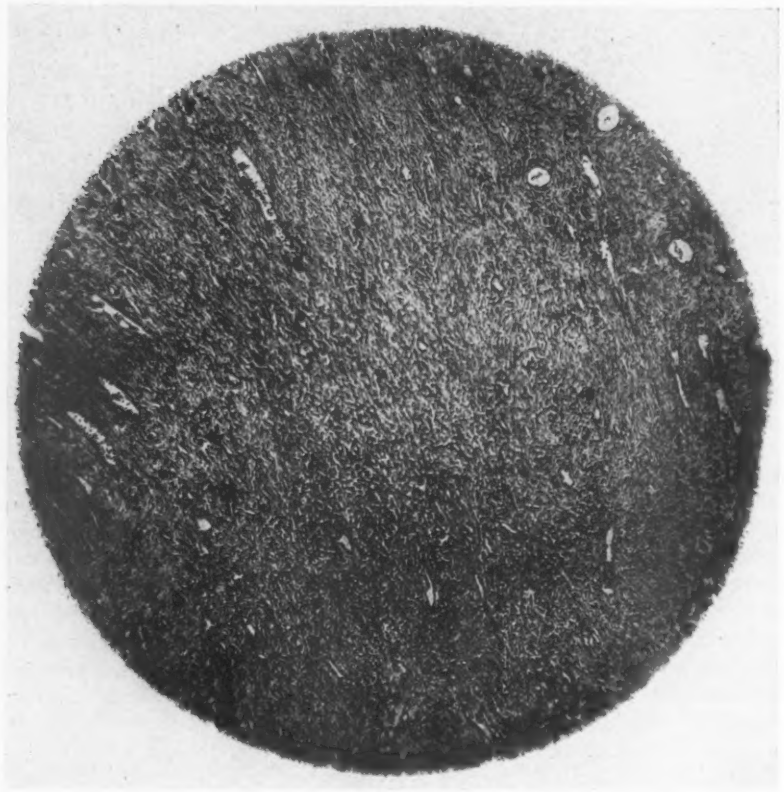


FIG. 4.—Photomicrograph of tissue from periphery of tumor, showing whorls of fibrous tissue with apparently benign appearance. (x 75)

percentage of carcinomas of the liver that are primary is stated by Jaffe[3] as 1.5 to 3.0.

The mesenchymal tumors are far less common, originating in nonspecific elements of the liver, vascular or stromal. Tumors of vascular origin, particularly hemangiomas comprise the greater part. An accurate count of the reported cases of primary sarcoma is almost impossible because of the confusion in classification, the histologic similarity between highly anaplastic carcinoma and

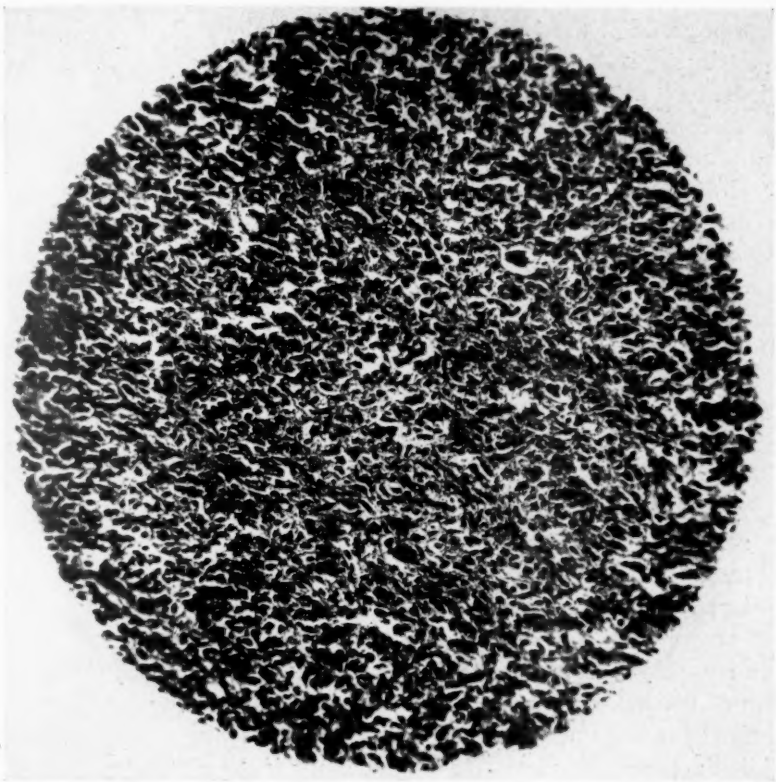


FIG. 5.—Photomicrograph of tissue from sarcomatous central area of tumor, showing extreme cellularity, hyperchromatism of nuclei, and multinucleated cells. (x 200)

sarcoma, and the difficulty in some instances of ruling out origin of the tumor from the diaphragm or thoracic wall. Thus, Jaffe,[3] who reviewed the literature in 1924, collected 48 cases, while Goldstein,[4] in the same year, collected 59. Miller[5] collected 30 additional cases for his review in 1939. It is probable that the total number of histologically-studied cases of primary sarcoma is not more than 100 at the present time.

Ewing[6] states that the true source of primary hepatic sarcomas has never been actually traced, although various opinions have been voiced in the literature. These have included origin from the connective tissue about the blood vessels or acini (Arnold[7]); the cellular elements of the vessels (Delepine[8]);

the perilymphatic connective tissue (Byrom[9]); the normal connective tissue (Demel[10]); the new connective tissue in portal cirrhosis (29 per cent of cases were associated with cirrhosis according to Jaffe[3]) or syphilitic cirrhosis (Hedren[11]); the wall of a chronic abscess (Goldstein[12]); the wall of an echinococcus cyst (De Vecchi[13]); or a preëxisting cavernoma (Marx[14]). Dubs[15] reported a case of spindle cell sarcoma in a 26-year-old girl who died six months after an injury to the liver. In the authors' case the tumor may have arisen from the connective tissue of the round ligament.

Fibrosarcomas of the liver do not differ pathologically from those found elsewhere in the body. According to Jaffe,[3] they are not prone to produce metastases.

The symptoms and signs of malignant tumors of the liver are subject to wide variation. The patient may be asymptomatic; there may be a history merely of an upper abdominal mass; other patients, usually those with late lesions, may show evidence of cirrhosis, jaundice, ascites, and cachexia. Jaundice depends upon the location of the tumor with respect to the large biliary ducts. Pain in the lumbar, flank, epigastric, or shoulder regions is usually a late symptom and has been attributed to distention of the capsule.

Only after thorough clinical and laboratory studies have failed to disclose a primary tumor elsewhere, should the possibility of primary hepatic tumor be considered. Certain preoperative differentiation between carcinomatous and sarcomatous lesions is not possible unless peritoneoscopy, with biopsy of the tumor mass for microscopic study, is performed. As in the authors' case, the diagnosis of primary hepatic sarcoma is usually not thought of, let alone actually made.

The treatment of primary tumors of the liver is surgical resection. According to Warvi,[2] normal and neoplastic liver tissue are both highly radioresistant, and the severe systemic reactions resulting from irradiation of the upper abdomen contraindicate roentgenotherapy. On the other hand, if the general condition of the patient is poor; if distant metastasis or regional lymph node metastasis at the liver hilum can be demonstrated; if the growth involves the major bile ducts and blood vessels at the hilum; if the remaining area of liver appears involved or if marked reduction of hepatic function indicative of extreme parenchymal involvement exists, then resection likewise is contraindicated.

The anesthetic should provide good relaxation, be nontoxic to the liver, and permit maximal oxygenation of the blood. For this purpose spinal or cyclopropane anesthesia are suitable.

Adequate exposure for resection may be obtained by either a transverse or transrectus incision. Exposure may be further facilitated by hyperextension of the spine, severance of the falciform or triangular ligaments, and insertion of an inflated rubber glove to keep the liver down from the diaphragm.

The various methods of hepatic resection merely represent different ways of dealing with the major technical problem of control of hemorrhage. An incision which radiates out from the liver hilum will reduce the number of severed vessels and ducts, and thereby reduce hemorrhage. Undue hemorrhage

can be controlled temporarily by manual pressure on the aorta above the celiac axis. The hepatic artery may be compressed within the hepatoduodenal ligament by finger pressure or by a rubber padded clamp. This procedure, if employed for more than ten minutes, is apt to be followed by a profound fall in blood pressure. It may be employed for a few minutes as a life-saving procedure in the face of violent uncontrollable hemorrhage, but, as emphasized by Tinker,[16] is undesirable as a routine. As an aid in the control of moderate hemorrhage, Warvi[17] has summarized the following measures: digital compression of the cut liver edge; tourniquet of the liver proximal to the bleeding edge; tamponade of the bleeding surfaces; application of spring clamps or rubber-shod intestinal clamps near the edge; or controlling the oozing with adrenalin solution 1:1000, making the larger bleeding vessels discernible enough to be clamped and ligated. To these measures may be added the use of thrombin, topically applied as a powder or solution. Although to date there are no reports of the use of thrombin in humans to control bleeding in hepatic resection, animal experiments indicate that this substance may be of great aid in operations upon the liver. Tidrick, and coworkers,[18] report its successful use in the control of persistent oozing from the gallbladder bed of the liver following cholecystectomy.

Early attempts at removal of hepatic tumors were made by employing elastic ligature compression of the tumor stump, usually with extraperitonization of the stump (Cousins,[19] 1874). The tumor was then cut distal to the ligature, or else allowed to slough off. Another early method (Clementi,[20] 1890)) featured the application of one or more clamps at the tumor base which were left in place. In some instances the entire clamps were exteriorized (Lapoint,[21] 1897), while in others only the handles were exteriorized through a stab incision (Kocher,[22] 1902).

In the actual resection of liver tissue not only has the scalpel been used, but also simple cautery (Escher,[23] 1886) and electrocautery (McLean,[24] 1929). Suturing of the liver with a blunt needle for hemostasis just proximal to the contemplated line of resection has been advocated (Kousnetzoff and Pensky,[25] 1896). Raw surfaces should preferably be approximately directly, as in the authors' case, but, when this is not entirely feasible, omentum or gauze packing may be sutured in between.

According to Pickrell and Clay,[26] when the tumor occurs in the left lobe of the liver, it is preferable to do a complete lobectomy rather than a local removal of the tumor. These authors cut the falciform ligament close to its diaphragmatic attachment to aid in exposure and delivery, apply hemostatic sutures at the division between right and left lobes, resect the left lobe, and reperitonize the raw area with the flap of falciform ligament. They claim the advantages of wider resection of the lesion without embarrassment of hepatic function, decreased bleeding, and complete peritonization of raw areas.

The most important general postoperative complications following this type of surgery are metabolic, consisting early of "liver shock" or hepatorenal syndrome and later of malnutrition. These may be prevented in most instances by proper dietary management. Locally, sinuses draining bile, necrotic slough,

or pus may persist in the wound for varying lengths of time. According to Warvi,[17] secondary hemorrhage has occurred in only 2 per cent of cases of hepatic resection since the beginning of the century. Postoperative ileus, atelectasis and pneumonitis may occur, as in other upper abdominal operations. The incidence of pulmonary embolism is not outstanding following hepatic resection. Its unfortunate occurrence in the authors' case is regarded as one which might have followed any upper abdominal operation for cancer in an elderly patient.

SUMMARY AND CONCLUSIONS

1. A case of primary fibrosarcoma of the liver, in which the lesion weighed 5,200 Gm., is reported in detail. The patient died suddenly on the 11th postoperative day, probably of pulmonary embolism.

2. The various methods of resection of hepatic tumors are discussed. A knowledge of these is essential in order to deal successfully with the unusual technical problems which these tumors may present.

REFERENCES

1 Yeomans, F. C.: Primary Carcinoma of the Liver. J. A. M. A., **64**, 1301, 1915.
2 Warvi, W. N.: Primary Neoplasms of the Liver. Arch. Path., **37**, 367, 1944.
3 Jaffe, R. H.: Sarcoma and Carcinoma of the Liver following Cirrhosis. Arch. Int. Med., **33**, 330, 1924.
4 Goldstein, H. I.: Primary Malignant Tumors of the Liver. M. J. and Rec., **120**, 120, 1924.
5 Miller, J. K.: Primary Sarcoma; Endothelioblastoma; Case Report. Am. J. Surg., **44**, 458, 1939.
6 Ewing, J.: Neoplastic Diseases. Fourth Ed., Philadelphia. W. B. Saunders Co., 1940, p. 752.
7 Arnold: Ziegler's Beiträge z. path. Anat., **8**, 123, 1890; quoted by Ewing.[6]
8 Delepine: Trans. London Path. Soc., **42**, 161, 1891; quoted by Ewing.[6]
9 Byrom: Quoted by De Vecchi[13] and by Ewing.[6]
10 Demel: Z. p. 1. sc. med., Torino, **24**, 273, 1900; quoted by Ewing.[6]
11 Hedren: Quoted by Saltykow: Sarcoma and Carcinoma of the Liver. Cor. Bl. f. schewiz. Aerzte, **44**, 385, 1914; quoted by Jaffe.[3]
12 Goldstein: Internat. Clin., **2**, 73, 1921; quoted by Jaffe.[3]
13 De Vecchi: Soc. Med. Chir. de Bologna 6, June, 1908; quoted by Jaffe.[3]
14 Marx, H.: Centralbl. f. allg. Path., **15**, 433, 1904; quoted by Ewing.[6]
15 Dubs: Deutsch. Ztschr. f. Chir., **138**, 1, 1917; quoted by Jaffe.[3]
16 Tinker, M. B. and Tinker, M. B., Jr.: Resection of Liver: Conditions Favorable for Operation; Methods; Experimental Studies. J. A. M. A., **112**, 2006, 1939.
17 Warvi, W. N.: Primary Tumors of the Liver. Surg., Gynec. and Obst., **80**, 643, 1945.
18 Tidrick, R. T., Seegers, W. H., and Warner, E. D.: Clinical Experience with Thrombin as a Hemostatic Agent. Surgery, **14**, 191, 1943.
19 Cousins: Quoted by Warvi.[17]
20 Clementi: Quoted by Warvi.[17]
21 Lapoint: Le Bull. Med., 1897, p. 883; quoted by Warvi.[17]
22 Kocher: Quoted by Warvi.[17]
23 Escher: Quoted by Warvi.[17]
24 McLean, A. J.: Bovie Electrosurgical Current Generator: Some Underlying Principles and Results. Arch. Surg., **18**, 1863, 1929.
25 Kousnetzoff and Pensky: Quoted by Warvi.[17]
26 Pickrell, K. L., and Clay, R. C.: Lobectomy of the Liver. Arch. Surg., **48**, 267, 1944.

SIMULTANEOUS REPAIR OF PERIPHERAL NERVE AND SOFT TISSUE DEFECTS IN THE FOREARM

MAJOR FRANK F. ALLBRITTEN, JR.
MEDICAL CORPS, ARMY OF THE UNITED STATES

EARLY INITIAL SURGERY, blood replacement therapy, bacteriostatic drugs, and reparative surgery have been responsible for preserving many seriously injured extremities in World War II. Often these extremities have suffered extensive soft tissue loss and have presented problems in reconstructive surgery. Soft tissue defects healed with extensive cicatrix and covered by split-skin grafts are neither sightly nor functionally adequate. Underlying tendons and muscles are often adherent and their function is impaired. Concomitant bone and nerve injuries are usual and attempts at repair made through scar tissue often end in failure (Fig. 1, A and B). Therefore, it has become an accepted measure to excise all scar tissue from the extremity and to fill the defect with a graft of more normal fat and skin before considering additional reconstructive efforts.

Several weeks may be required to cover the soft tissue defects in the forearm by use of a tubed graft. A "pattern" or "flap" graft from the abdominal wall can usually be completed in a period of one month. However, before the wound can be opened again for reconstructive procedures several additional weeks elapse while the blood supply to the transplanted tissues becomes established.

It was thought that if the soft tissue defect could be corrected and the injured nerve repaired at a single operative procedure the time of hospitalization of the patient could be shortened considerably. Certain other advantages would be offered by such a procedure. The early replacement of an encircling, binding, cicatrix of the forearm by more normal tissue would greatly improve the nutrition of the hand, edema would be lessened, the soft tissues would become more supple. Release of scar tissue adhesions would aid in early restoration of full extent of joint movement and permit useful function of the extremity to be resumed. In addition to these considerations the time factor influencing nerve regeneration must be taken into account. Nerve repair soon after injury offers optimum conditions for regeneration. The prolonged delay in nerve repair that is so common in extensive soft tissue injuries results in increased fibrosis in the distal nerve segment and atrophy of muscle tissue that ultimately is manifest by impaired or complete failure of return of function.

Patients with extensive soft tissue defects in an extremity often have extensive loss of nerve substance. Approximation of unscarred nerve ends without tension then requires an extensive mobilization of the nerve. In the arm, forearm, and wrist the defect is usually overcome by transplant of the nerve across a joint in flexion. Total time of immobilization of the joint can be reduced appreciably if the healing of the soft tissue defect and the site of nerve suture can occur simultaneously.

In consideration of these possibilities the following plan of treatment has been used. The first stage consists of the following: (1) The scar tissue is meticulously excised; (2) the nerve is explored, mobilized, transplanted and sutured (Fig. 1C); (3) a pattern flap is raised from the abdomen to cover the

FIG. 1A

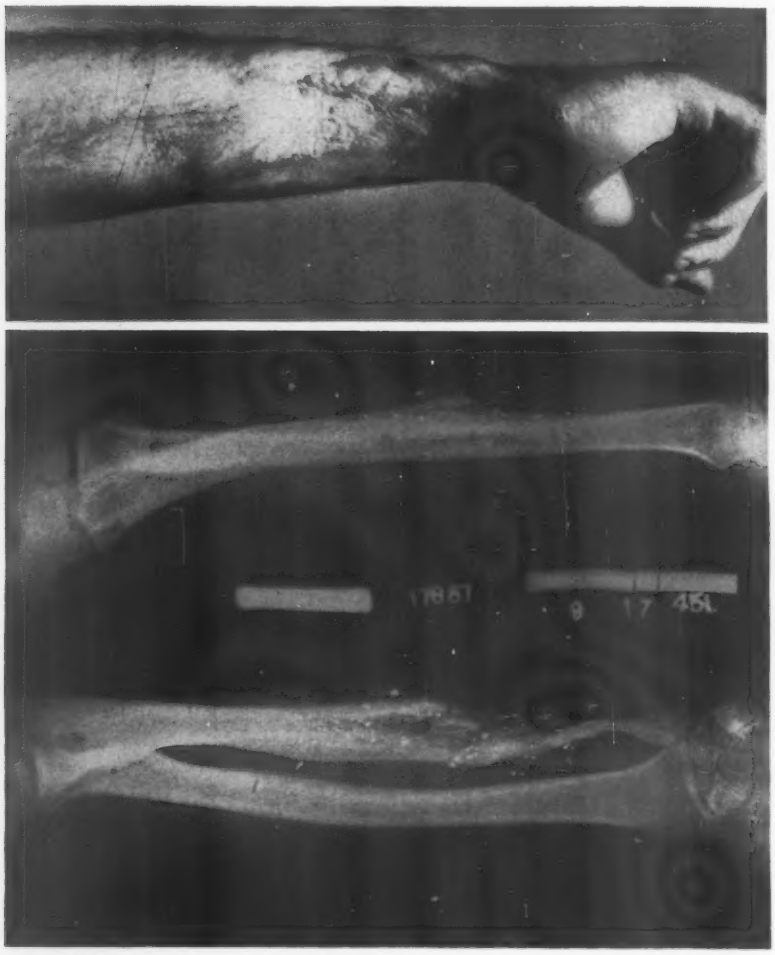


FIG. 1B

FIG. 1A and B.—The large soft tissue defect and bone destruction resulting from a rifle bullet wound of the forearm. Complete paralysis of ulnar nerve. Split-thickness skin graft had been applied during early reparative surgery.

soft tissue defect; (4) the skin and subcutaneous tissue of the abdominal wall is mobilized about the site from which the flap was raised and is closed by retention sutures (Fig. 1D); (5) the raised pattern flap is sutured to the defect in the forearm over a broad area and opposing margins of the abdominal

and forearm wounds are carefully approximated in order to completely close the wound (Fig. 1E); and (6) the forearm is immobilized in a suitable position with an adhesive dressing and the joints of the wrist and the hand are free for active movements. The skin sutures may be removed in seven days and the retention sutures removed in fourteen days. At the end of this

FIG. 1C

FIG. 1D

FIG. 1E

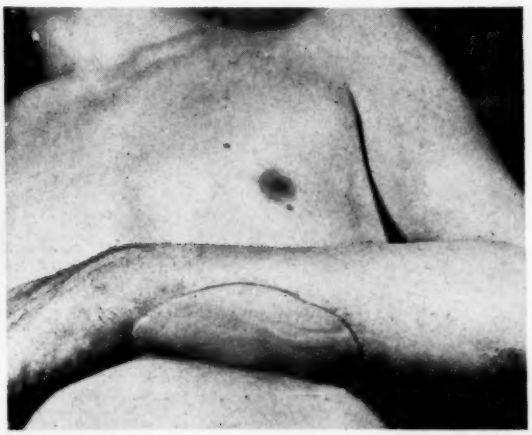


FIG. 1F

FIG. 1C.—All scar tissue has been excised. The ulnar nerve has been transplanted anterior to the elbow joint and a defect of 10 centimeters in the continuity of the nerve closed by suture of the nerve ends.

FIG. 1D.—The abdominal flap cut to the pattern of the defect is raised. The edges of the abdominal wound have been widely mobilized and approximated with retention sutures.

FIG. 1E.—The flap graft is sutured into position. The opposite edge of the defect in the forearm is sutured to the adjacent edge of the abdominal wound to accomplish a completely closed wound.

FIG. 1F.—Soft tissue defect closed and nerve repaired six weeks after beginning of operative procedure.

period the wound should be firmly healed. It has been customary to use penicillin prophylactically during this period.

The second stage is undertaken in three or four weeks. It consists of the following parts: (1) Division of the pedicle flap at its site of attachment to the abdomen; (2) suture of the abdominal wound; and (3) suture of flap to edge of defect in the forearm. Skin sutures can be removed in seven days and

FIG. 2

FIG. 3

FIG. 2.—End-result of combined repair of median nerve and soft tissue defect. Total time of five weeks from beginning of procedure until all sutures were removed. Subsequent examinations have shown normal progress of nerve regeneration.

FIG. 3.—End-result in patient with combined ulnar nerve suture and repair of soft tissue defect at wrist. A previous attempt at nerve suture through the cicatricial tissue had failed for the operative wound disrupted. Total time of six weeks from the beginning of the procedure to its completion. Follow-up examinations have shown usual progress in nerve regeneration.

the movement of all joints started (Fig. 1F). Penicillin has been given prophylactically until the wound has healed.

The use of this method has produced satisfactory results from the aspect of nerve regeneration and repair of the soft tissue defects. The accompanying illustrations and legends give representative cases.

SUMMARY

Nerve repair combined with pattern flap grafts to soft tissue defects in the forearm is described.

The advantages of this procedure are: (1) A decrease in the period of hospitalization; (2) an early nerve repair; and (3) a decrease in the time of immobilization of the joints of hand and elbow.

REFERENCES

Brown, J. B., Cannon, B., Graham, W. C., Lischer, C. E., Scarborough, C. P., Davis, W. B., and Moore, A. M.: Direct Flap Repair of Defects of the Arm and Hand. ANNALS OF SURGERY, **122**, 706–715, October, 1945.

Bunnell, S.: Surgery of the Hand. Philadelphia, J. B. Lippincott Company, 1944.

Highet, W. B., and Saunders, F. K.: Effects of Stretching Nerves after Suture. Brit. J. Surg., 30: 355–369, April, 1943.

Holmes, W., and Young, J. Z.: Nerve Regeneration after Immediate and Delayed Suture. J. Anat., **77**, 63–96, 1942.

Subcommittee on Neurosurgery, Division of Medical Sciences of the National Research Council: Neurosurgery and Thoracic Surgery. Philadelphia, W. B. Saunders Company, 1943.

BACTERIOLOGIC STUDY OF BURN WOUNDS*

A COMPARISON OF THE BACTERIAL FLORA OF BURN WOUNDS OF PATIENTS TREATED WITH SULFONAMIDES OR PENICILLIN

JOHN L. LANGOHR, M.D., CORA R. OWEN, PH.D., AND OLIVER COPE, M.D.
BOSTON, MASSACHUSETTS

FROM THE DEPARTMENT OF SURGERY OF THE HARVARD MEDICAL SCHOOL AND THE SURGICAL SERVICES AT THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASSACHUSETTS

PART I

AS LONG AS the contaminating bacteria of a burn wound are able to flourish, the resulting infection will be *the* deterrent to the healing of the wound. These bacteria do not flourish in a shallow, partial-thickness wound and, therefore, infection and retarded healing are not to be countenanced. It is suspected that this shallow wound does not nourish them. Prompt healing, therefore, is anticipated and the claims for various methods for expediting healing of the partial-thickness burn wound are discounted. In a full-thickness burn wound the bacteria flourish and will unless something is done to starve, kill or remove them.

To do one or more of these has been attempted by many methods, both local and systemic, and none has been entirely successful. Agents in the form of solvents, such as Dakin's solution, corrosive and coagulating chemicals and the more selective vital dyes have been applied to the wound surface; judged to discourage the bacterial growth and the infectious process, in their toxicity they have proved damaging to viable cells. The sulfonamides applied locally do not damage viable cells but, limited to an antistreptococcal specificity, they have failed to block the generation in the wound of other bacterial species equally insidious. Every effort to control the less susceptible organisms by increasing the local concentration of a sulfonamide drug is thwarted by its rapid absorption from the wound and a rise in concentration to toxic levels of the drug in the body fluids and renal shut-down. So predictable is this absorption that only in burns of minor extent can sulfonamides be applied in a medium permitting high and broadly useful concentrations.† The drug,

* The work described in these papers was done under a contract, recommended by the committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

† The possibility that the rapid absorption of sulfonamides from burn wounds might result in toxic levels of the drug in the extracellular fluid was reported in 1941 by Hooker and Lam.[1] Renal shut-down, with sulfonamide poisoning, was observed in two patients treated at the Massachusetts General Hospital in 1942. An extensively burned patient whose wounds were sprayed with triethanolamine containing 3 per cent sulfadiazine (Pickrell's solution[2]) developed a blood level of 37 and 54 mg./100 cc. of sulfadiazine on the 3rd and 5th days after injury and the initial application. Complete urinary suppression occurred on the 2nd day, and was unrelieved. Death in uremia occurred on the 6th day. Sulfanilamide powder applied to a large full-thickness wound of the second patient (Case 76) on the 11th day after injury was followed 24 hours later by a blood level of 21 mg./100 cc. Renal damage contributed to the death on the 27th day. The failure of sulfonamides in certain ointments to rise to toxic levels in the body fluids[3, 4] is to be ascribed to a sluggish release of the drug from the ointment base. No more effective a concentration of the drug is to be expected to reach the fluid recesses of the wound from such ointments than from internal administration.[5, 6]

systemically administered, fares no better; it has imposed upon it the same limitation of toxicity as when locally applied and is only successful in controlling the invasive infection of the streptococcus.

All of these agents, even including the most promising—the sulfonamides—have been discarded because of their toxicity or failure, and without elucidating the rôle which the burn slough of the wound plays in the growth of the bacteria. The necrotic tissue coagulum, deprived of its blood supply, should be fertile soil. It is also conceivable that this coagulum is impervious to antibiotic agents while at the same time permitting penetration of the bacteria; or it might contain drug inhibitors similar to those of the sulfonamides encountered in pus.

Such were the tools and the understanding of their abilities for attempting the control of infection at the time of the advent of penicillin. It was tempting to hope that penicillin would succeed where the sulfonamides had failed since it was reported nontoxic at any dosage and had wider specific antibacterial properties. The absence of toxicity at any dosage level would be peculiarly valuable for the extensively burned patient threatened with dehydration. The initial experience with penicillin in patients with infections other than burns showed it to have a specificity against the streptococcus equal to that of the sulfonamides as well as a specificity against the staphylococcus. It was wise however in view of the disappointing performance of the sulfonamides to be wary of penicillin's power to control the infection of the full-thickness burn wound.*

In our wariness of penicillin and desire to achieve the earliest possible healing of the full-thickness burn wound it was decided to combine the use of penicillin with prompt surgical excision and grafting of the wound. Surgical excision of the full-thickness burn wound should reduce the number of contaminating bacteria and eliminate necrotic tissue. The base left after excision would undoubtedly be contaminated, but since it would be composed of viable cells, any graft laid upon it would not only prevent further contamination but should proceed to heal without being forestalled by infection. To have the ideal base upon which to place the graft, excision of the burn wound down to viable tissue should be done immediately after injury. With the passage of time the contaminating bacteria within the burn slough would have a chance to multiply and, therefore, the longer the delay after injury, the greater the number which would inevitably be transferred to the excised base during the operative procedure. Also, with the passage of time an inflammatory reaction would appear beneath the necrotic skin in the living

* It is not possible by quoting the literature available in 1943, the time when this project was initiated, to give proper credit for the ideas and help upon which we drew freely. Information available at that time and currently throughout the war was promptly disseminated by bulletin to each group of investigators by the Office of Scientific Research and Development. An adequate survey of the literature is not intended. In the setting-up and conduct of this project, we are particularly indebted for advice to Dr. Champ Lyons, Dr. Rene J. Dubos, Dr. Chester S. Keefer, and Dr. Frank L. Meleney.

tissues which form the base left after excision. Any inflammation should be unhealthy for the successful take of the graft.

The full-thickness burn wound of limited extent has been excised immediately after injury and the defect closed with a graft. The excision and grafting of extensive full-thickness wounds has had to be delayed because of the precarious physiologic state of the patient and because unburned skin for the grafting was lacking. The excision and grafting of both circumscribed and extensive wounds has also been delayed because this project was set-up with the needs of the Armed Services in view and because the postulated conditions of warfare indicated that it would not be possible to operate immediately upon a burn casualty. The delay facing the casualty suggested that an arbitrary interval of from four to seven days between injury and excision and grafting should be tried in some of the cases.[7]

Penicillin was administered systemically to all patients whether excision and grafting was immediate or delayed. Although, admittedly, two therapies were being tried at the same time, and it might prove difficult to ascribe to each its share of credit, the drug was given advisedly to give the operation all possible support and, in those patients in whom time was allowed to elapse between injury and surgical excision, to afford the opportunity to judge the efficacy of penicillin in holding infection in abeyance.

The study has included a comprehensive survey of the bacterial flora of burn wounds and its alteration under penicillin therapy and of certain changes in metabolism of the organisms, such as the development of a resistance to penicillin during the course of its administration. Dissemination of the organisms of the wound through the blood stream and urinary tract and certain aspects of the metabolic response of the host, including the development of a specific immunity, have been studied as well.

Penicillin was not withheld from alternate cases for purposes of control; it was believed that those patients with comparable wounds who had been treated with sulfadiazine systemically in the year previous would serve as acceptable controls. The majority of these patients were those studied under the Contaminated Wound Project of Doctor Meleney by Drs. Champ Lyons and F. W. Rhinelander at the Massachusetts General Hospital.[8] The bacteriologic technics of Doctor Lyons and this study were identical.

To achieve clarity of presentation the data of the study have been divided into four papers. In the first, the nature of the bacterial contamination and subsequent flora found in partial and full-thickness burn wounds in patients treated with either penicillin or sulfadiazine is described. In the second, the natural occurrence among bacteria of penicillin resistance and inhibition and the development of penicillin resistance in the flora of the burn wounds of patients treated with penicillin is recounted. Presented in the third and fourth papers are the aspects peculiar to the staphylococcus and streptococcus. Brief comments only are made in conclusion of the first three parts. Discussion of the observations, including the clinical significance, is delayed until the end of the fourth part.

METHODS

Immediately upon entry to the hospital, each patient was placed in an isolation room in the Emergency Ward where every precaution was taken to avoid further contamination. The burn wounds were inspected, their location and depth charted. They were then covered, without débridement or cleansing, with a firm protective dressing of petrolatum impregnated, fine-meshed gauze, thick dry cotton and an elastic bandage or a towel. Subsequent changes of dressing were made in an operating room under aseptic precautions.

The patients were accommodated in single rooms on an isolation floor where supervising nurses were in constant attendance. Occasional bacterial counts of the air in these rooms showed a number and variety of organisms comparable to those recovered from the air of single rooms on a floor caring only for uninfected surgical cases; from the air of rooms in another part of the hospital containing infected cases cared for without special precautions were recovered a wider variety of pathogenic organisms with more than ten times the number of colonies.*

The burns were arbitrarily divided into areas or "wounds." A culture was taken of each wound on admission and at each subsequent change of dressing until healing occurred. The cultures taken on the day of injury (O-day) in the majority of the sulfonamide-treated cases were of dead epidermis removed from the wounds. All other cultures, including those of O-day of the penicillin-treated, and the remainder of the sulfonamide-treated cases, were taken by rubbing the exposed surface of the wound with dry sterile cotton swabs.

The technics used for isolation and identification of the organisms were essentially those established by Meleney[8] for the various units of the Contaminated Wound Project under the Committee on Medical Research of the Office of Scientific Research and Development. Anaerobiasis was secured by the chromium-sulfuric acid method of Rosenthal,[11] as modified by Mueller and Miller.[12]

Isolation and identification of all morphologic types, seen microscopically, were attempted, selective media, especially those for the suppression of gram-negative bacilli,[13] being resorted to when necessary. The gram-negative bacilli

* Colebrook,[9] and Cruikshank[10] have repeatedly called attention to the frequency of the spread of organisms from one burned patient to another on an open ward. Strains of streptococci, recognizable by their Griffith-type and sulfonamide resistance, were traced in the wounds and also in the dust of the room. It was in order to reduce such cross and continued contamination that the patients included in the present study of wound flora were cared for in isolation rooms under special precautions and had their dressings changed, each wound separately, with aseptic technic only in the operating room. These precautions resulted in some patients in preventing an organism, for example a staphylococcus, from spreading from one wound to an adjacent one in the same patient. On the other hand, in spite of all precautions, evidence was occasionally obtained of the spread of a bacterial strain from one patient to another. A morphologically typical diphtheroid, causing a green discoloration of blood agar with a fruity odor on growth, first isolated from one patient, spread during the course of two weeks to three other patients.

were identified to the genus. The presence of aerobic gram-positive sporulating and nonsporulating (diphtheroid) bacilli was merely recorded. The staphylococci were also examined for color, production of hemolysis on five per cent horse blood agar, and the power to coagulate normal human plasma; the streptococci for type of hemolysis produced on five per cent horse blood agar, the Lancefield groups (A, B, and C, only) if *beta* hemolytic, and "dreft" (bile) solubility for differentiation from the pneumococcus if *alpha* hemolytic[14]; and the *Clostridia* for species, as far as possible according to Spray's "Tentative Key to the Sporulating Anaerobes."[15]

OBSERVATIONS

The data to be given in this study of bacterial flora of burn wounds are limited to those obtained from patients who were in the hospital, and under observation, from the time of onset of chemotherapy until the wounds were healed or the study ended. Fifty-four patients were observed under systemic penicillin therapy and 38 under systemic sulfadiazine; these latter are the controls for the penicillin therapy. No patients were observed for any length of time who did not receive either form of chemotherapy; there are, therefore, no controls for both penicillin and sulfadiazine.

The penicillin dosage was relatively low in the first cases (100,000 units or less per day) and high in the later cases (250,000 to 500,000 units per day); in a few cases nearly 1,000,000 units per day were given over short periods. Sodium penicillin only was used; it was injected intramuscularly usually, occasionally intravenously. The dosage schedule for the intramuscular injections varied from two to four hours.

In the patients receiving sulfadiazine, the dosage was regulated by the blood level; it was maintained between 6 and 12 mg./100 cc. If a patient showed sensitivity to the drug it was stopped and the patient was dropped from the bacteriologic study at that time.

Cultures were obtained once a week from nearly all of the wounds; culturing was abandoned only when the wound was healed.

In addition to the study of the flora of the wound, the effectiveness of the penicillin therapy was also judged in certain cases by study of those of the blood stream and urinary tract.

(1) FLORA OF FULL-THICKNESS BURN WOUNDS UNDER PENICILLIN THERAPY (CHARTS 1A-C)

Twenty-eight patients with 80 full-thickness burn wounds were observed in the hospital from the day of injury until healing. Penicillin was administered to the patients for at least 49 days unless all of the wounds of a patient were healed before this time. The wounds were of varying extent. Some wounds were excised and grafted promptly; the grafting of others was delayed until after spontaneous separation of the slough. All cultures were planted from swabs which had been rubbed firmly on the wounds.

On the day of injury (O-day) an average of almost three bacterial strains

was recovered from each wound; from the 69 wound cultures on O-day 199 strains were recovered (Chart 1A). In the first two weeks there was an abrupt increase in the number of strains recovered so that by the 14th day an average of five strains was recovered from each wound (72 wounds cultured, 368 strains recovered). From the 3rd to the 7th weeks there was a gradual decrease in the number of all bacterial strains recovered, reaching an average of 4.2 strains per culture on the 49th day.

The increase in number of strains recovered in the first two weeks is primarily a reflection of an increase in the number of the streptococci and gram-negative bacilli, and to a less extent of the diphtheroids and aerobic spore forming organisms (*B. subtilis*) (Charts 1B and 1C). The gram-negative bacilli, after an abrupt rise in incidence in the first two weeks, continued to increase very little. The streptococci, after an initial abrupt increase, remained stationary in incidence during the remaining period of observation. The number of strains of *Clostridia* recovered varied but little over a period of seven weeks after a slight early increase. The strains of the staphylococci showed a slow and steady decrease in incidence throughout the period of observation.

The flora of the full-thickness wounds of patients who were admitted later than the day of injury but who had received no chemotherapy previously were also studied throughout a course of penicillin therapy which was started on admission and lasted for 42 days. Thirty-nine wounds in 19 patients who were admitted from 1 to 30 days after injury (average 7.2 days) were studied (Chart 2). The wounds varied in extent as did the amount of infection clinically apparent in the wound on entry and before chemotherapy. There was usually present a severe localized infection and occasionally an invasive process with cellulitis and lymphangitis. One patient had a positive blood culture of a *Staph. albus*. With the subsidence of the clinical infection, some of the wounds were excised and grafted. The cultures were by means of the swab technic.

The number of all bacterial strains recovered on admission was slightly lower than that found on the 7th day in the patients who were admitted and treated with penicillin beginning on the day of injury. Following onset of therapy there was immediately a decline rather than a rise in number. It was not until after the 30th day of therapy that the number of strains rose to that encountered in the previous group.

The incidence of certain individual bacterial strains was significantly either different from or similar to that encountered in the patients receiving penicillin from the day of injury. Of the differences, the staphylococci were found more often on the day of entry than at any time in those patients treated from injury; following onset of penicillin there was a sharp decline to the number of the previous group. The streptococci were also more often recovered and at their maximum on the day of entry. The incidence, however, of both *Clostridia* and the gram-negative bacilli was similar in the two groups of cases. The *Clostridia* scarcely varied while the gram-negative bacilli starting

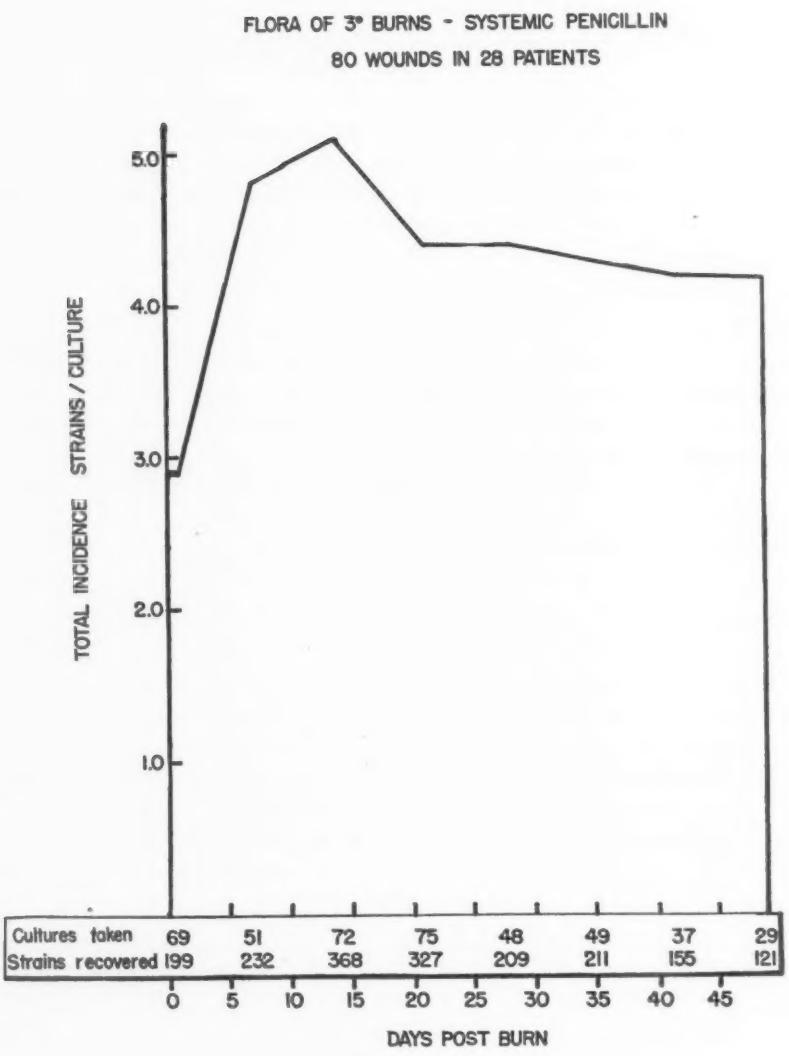

FLORA OF 3° BURNS - SYSTEMIC PENICILLIN
80 WOUNDS IN 28 PATIENTS
TOTAL INCIDENCE STRAINS / CULTURE
5.0
4.0
3.0
2.0
1.0
Cultures taken 69 51 72 75 48 49 37 29
Strains recovered 199 232 368 327 209 211 155 121
0 5 10 15 20 25 30 35 40 45
DAYS POST BURN

CHART 1A

CHART 1.—The Bacterial Flora of Full-thickness Burn Wounds in Patients Receiving Penicillin Therapy: Eighty wounds of 28 patients were followed from O-day through the 49th day unless healing had occurred previous to this time. Cultures were by the swab technic. The number of cultures planted on O-day, and within each subsequent seven-day period, and the number of strains recovered in these cultures are given at the bottom of each chart. Systemic penicillin was started on O-day and continued throughout the period of observation.

(A) Incidence of All Strains in All Cultures (Total Incidence: Strains per Culture): The abrupt increase in number of bacterial strains in the first two weeks and subsequent gradual decrease is evident.

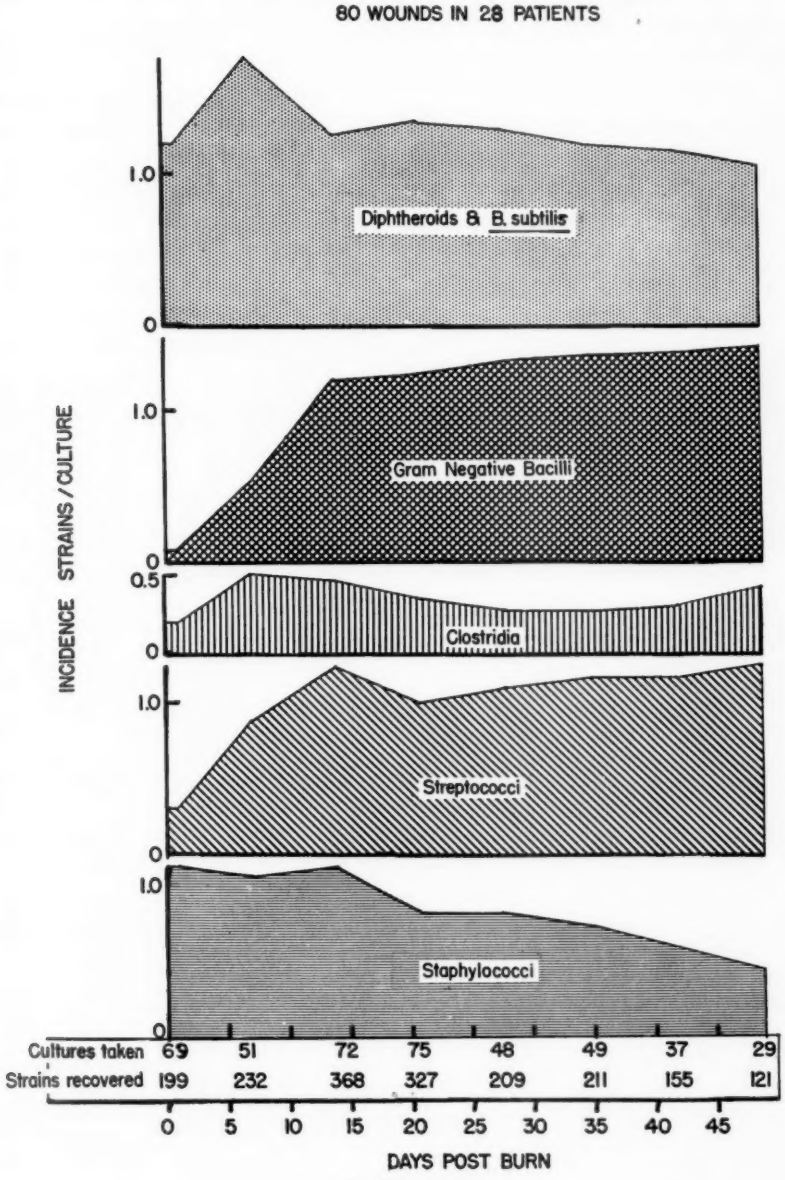


CHART 1B

CHART 1(B).—The Strains Recovered Plotted as Incidence or Number of Strains per Culture: Each strain is plotted in its appropriate bacterial group. The number of strains of staphylococci averaged slightly more than one per culture at entry and decreased gradually throughout the period of observation to less than one strain for every two cultures. The number of strains of streptococci, low on O-day, increased abruptly in the first two weeks and thereafter remained stationary in frequency. *Clostridia* were seldom recovered, and their incidence varied but little. Gram-negative bacilli, almost absent on O-day, increased abruptly in the first two weeks but only gradually thereafter. The incidence of diphtheroids and aerobic spore-formers (*B. subtilis*) increased slightly during the first week and gradually declined subsequently.

with but few increased abruptly in the second week of penicillin therapy and only slowly thereafter.

Bacteriuria.—A number of the patients with full-thickness wounds who were receiving systemic penicillin therapy developed signs and symptoms of lower urinary tract infection. The urine of several of these patients was cultured; various organisms, including gram-positive, were found but they were always of species present in the wounds of the same patient. All of the patients developing the infection had previously had in-dwelling catheters or been catheterized. The incidence of bacteriuria and urinary infection was not determined since the urine of the patients was not routinely cultured.

Bacteremia.—Blood cultures were made on 12 of the extensively burned patients, on 11 while they were receiving penicillin and on the 12th on the 2nd day after injury and before starting chemotherapy. This last patient and five of those on penicillin proved to have organisms in their blood. Four white staphylococci (2 coagulase-negative, 2 coagulase-positive), 2 *Clostridia* and 1 *B. proteus* were recovered. The same organisms were recovered from the wounds of the patient in each instance.

Most of the patients were sufficiently ill to arouse suspicion of invasive infection and the blood cultures were therefore taken. Two of the positive blood cultures found during the course of penicillin therapy were taken on the day after injury for chance information; both were positive, one showing *Clostridia* only, the other *Clostridia* and a *Staph. albus,* coagulase-negative. The cultures on the other eight were made at times of crisis; three were positive, two showing white staphylococci, coagulase-negative and positive, and the third *B. proteus.* The blood of the 11th case, cultured on the second day after injury, and before onset of penicillin therapy, contained a *Staph. albus,* coagulase-positive. A survey of the incidence of bacteremia in burns was not made.

(2) FLORA OF FULL-THICKNESS BURN WOUNDS UNDER SULFONAMIDE THERAPY (CHART 3)

The flora of 46 full-thickness burn wounds were studied in 25 patients who received sulfonamide therapy starting on the day of injury. Only 13 of the wounds were cultured on this day, and before the onset of chemotherapy, since 13 of the patients were victims of the Cocoanut Grove fire and the exigencies of their care discouraged the taking of cultures.[16] Sulfadiazine only was used systemically; a few patients had certain other sulfonamides applied locally at various dressings. The wounds were of varying extent. The first grafting was performed on the 24th day after injury when the slough had separated spontaneously. All wounds were followed as long as the patients were receiving systemic sulfonamides, or until healed. The 13 wound cultures accomplished on O-day were made from dead epidermis. All subsequent cultures were planted from swabs which were pressed firmly on the wounds in the manner used in the penicillin-treated patients.

The interpretation of the trend of the incidence of bacterial strains

recovered under sulfonamide therapy depends upon the significance ascribed to the numbers recovered in the cultures taken on O-day. A decrease in all bactrial strains in the first two weeks is shown (Chart 3). This is in contrast to the observations under penicillin therapy but its significance is to be discounted because of the discrepancies in the methods of culturing on O-day in

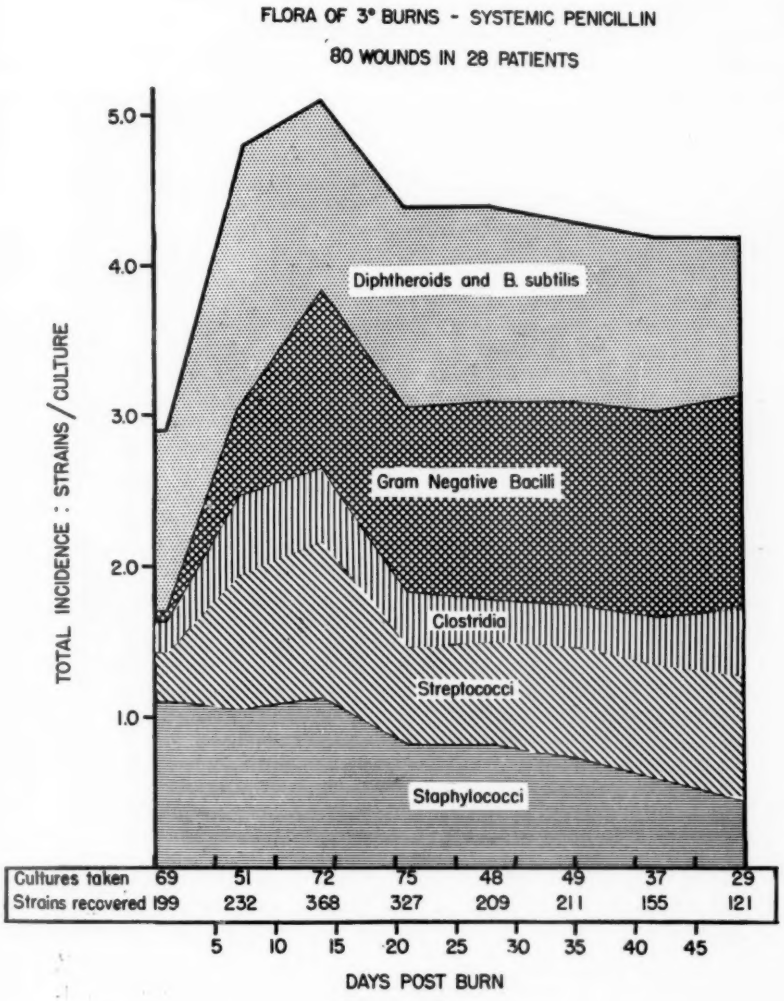


CHART 1C

CHART 1(C).—Composite of Charts 1A and B: Both the Incidence of Strains in the Individual Bacterial Group and the Part which each Plays in the Total Incidence: The top (heavy) line shows the incidence of all strains recovered and is in the identical position as in Chart 1A. The area occupied by each bacterial group is planometrically the same as that in Chart 1B. The zero line of each group other than that occupying the bottom position (staphylococci in this instance) is distorted by the top line of the group or groups beneath. (All of the subsequent charts of bacterial incidence are composed in this manner.)

the two groups and because the number of sulfonamide-treated patients cultured on O-day was small (only 12 patients with 13 wounds).

If one discounts the O-day findings then the incidence of bacterial strains shows a slow decrease in number in the first 35 days with an increased num-

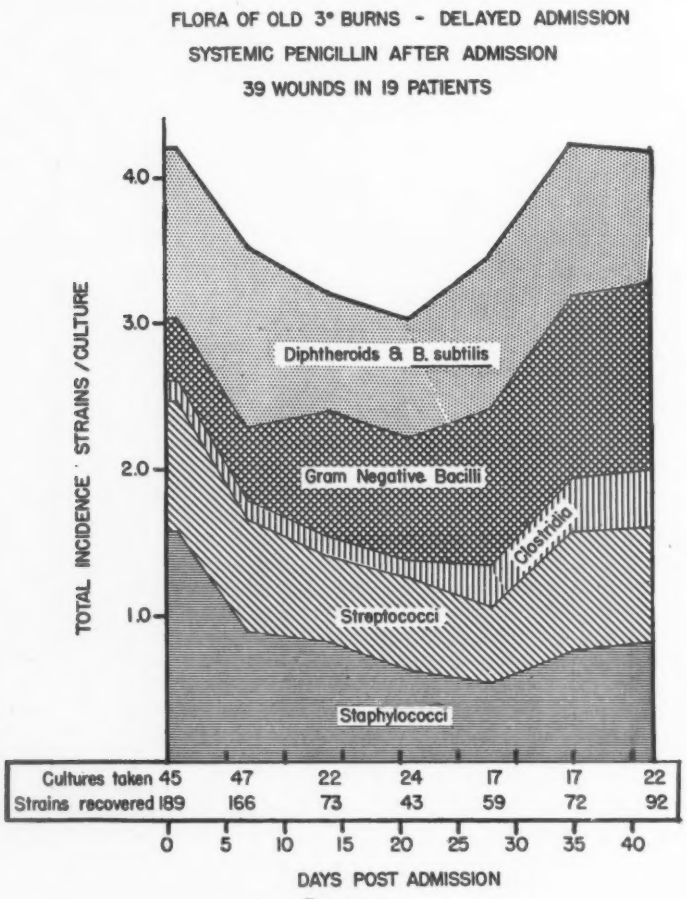


CHART 2

CHART 2.—The Bacterial Flora of Full-thickness Burn Wounds in Patients whose Hospital Admission and Penicillin Therapy were Delayed: Thirty-nine wounds of 19 patients were followed from day of entry to the 42nd hospital day unless healing had previously occurred. Admission varied from 1 to 30 days after injury (average 7.2 days). Cultures were by the swab technic. The number of cultures planted and strains recovered are given at the bottom of the chart, as in Chart 1, and all subsequent charts of bacterial incidence. Penicillin was started on the day of admission and continued throughout the period of observation.

ber later. The incidence of the staphylococci ran parallel to that of all bacterial strains. There is a consistent slow decline in the number of the streptococci with their complete disappearance on the 55th day. The *Clostridia* varied in incidence but little throughout the period of observation except for

disappearance on the 55th day. There is a gradual increase in the incidence of the gram-negative bacilli; it is slower than that encountered under penicillin therapy. The incidence of diphtheroids and aerobic spore-forming organisms (*B. subtilis*) fluctuated to some degree but the changes are probably not significant.

(3) FLORA OF PARTIAL-THICKNESS BURN WOUNDS UNDER SULFONAMIDE THERAPY (CHART 4)

The bacterial flora of 58 burn wounds of partial-thickness destruction were studied in 35 patients treated with sulfadiazine systemically. The

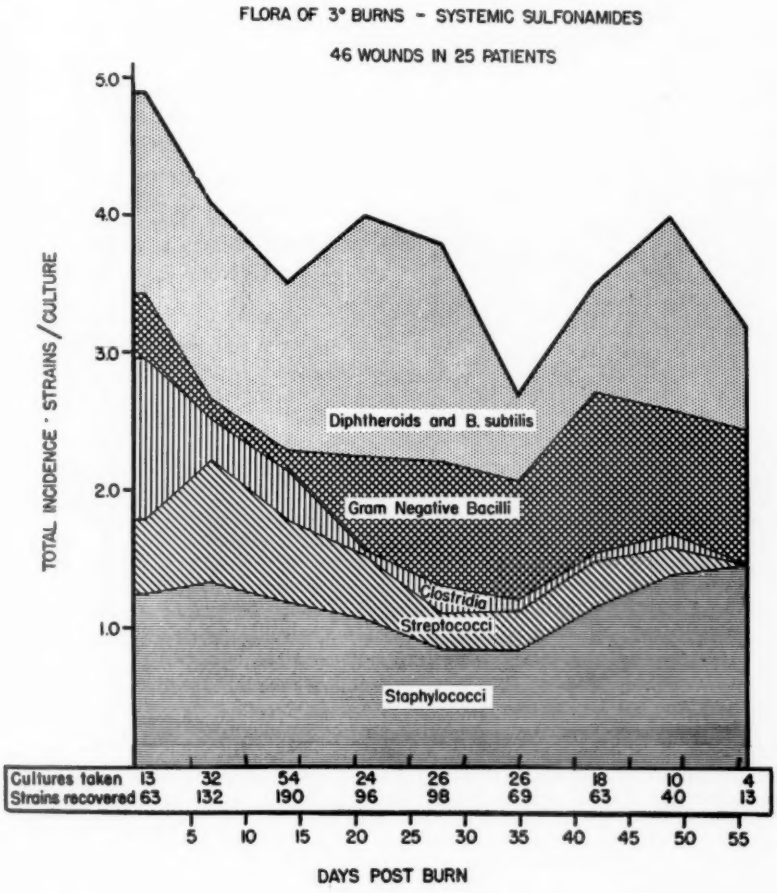

FLORA OF 3° BURNS - SYSTEMIC SULFONAMIDES
46 WOUNDS IN 25 PATIENTS
TOTAL INCIDENCE - STRAINS / CULTURE
5.0
4.0
3.0
2.0
1.0
Diphtheroids and B. subtilis
Gram Negative Bacilli
Clostridia
Streptococci
Staphylococci
Cultures taken 13 32 54 24 26 26 18 10 4
Strains recovered 63 132 190 96 98 69 63 40 13
5 10 15 20 25 30 35 40 45 50 55
DAYS POST BURN

CHART 3

CHART 3.—The Bacterial Flora of Full-thickness Burn Wounds in Patients Receiving Sulfonamide Therapy: Forty-six wounds of 25 patients were followed from day of injury to the 56th day, or until healed; however, 33 wounds of 13 patients (all victims of the Cocoanut Grove fire) were not cultured on the day of injury. Most of the cultures on the day of injury were of dead epidermis; all others were by swab technic. Sulfadiazine was started systematically on the day of injury and continued throughout the period of observation.

patients entered the hospital on the day of injury and were followed for not longer than 21 days. But 29 of the wounds were cultured before the onset of chemotherapy because 16 of the patients (with 29 wounds) were victims of the Cocoanut Grove fire. The wounds were of varying extent; all were open with ruptured blisters. The depths varied from superficial to deep intermediate- or almost full-thickness. In addition to the systemic sulfadiazine, sulfonamides were applied locally to a few of the wounds at the initial and later dressings. The majority of the 29 wound cultures made on the day of injury were grown by dropping dead epidermis into the culture medium; thereafter all cultures were made from swabs.

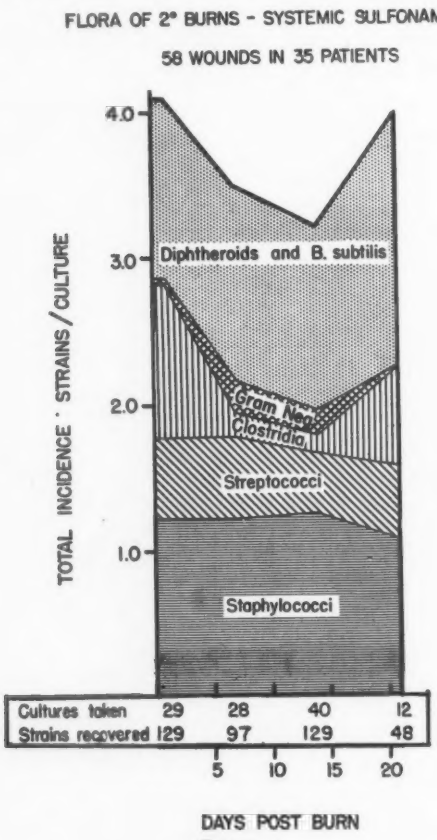


CHART 4

CHART 4.—The Bacterial Flora of Partial-thickness Burn Wounds in Patients Receiving Sulfonamide Therapy: Fifty-eight wounds of 35 patients were followed from day of injury to the 21st day, or until healed; however, 29 wounds of 16 patients were not cultured on day of injury. The majority of the cultures on the day of injury were from dead epidermis; all others were by swab technic. Sulfadiazine was started systemically on the day of injury and continued throughout the period of observation.

The incidence of all bacterial species encountered approximates that of the full-thickness wounds under sulfonamide therapy (Chart 4; cf. Chart 3). The only significant differences found in the partial- as compared with the full-thickness wounds are a slightly lower initial contamination and an increase in the third week in the incidence of the *Clostridia*.

(4) FLORA OF PARTIAL-THICKNESS BURN WOUNDS UNDER PENICILLIN THERAPY (CHART 5)

The bacterial flora of 35 wounds of partial-thickness were studied in 18 patients who were receiving penicillin systemically. The wounds were of varying extent, all open and ruptured blisters, and were of varying depths from superficial to nearly full-thickness. All were cultured on injury and were followed until the 21st day, or until healed. The cultures were all by swab technic.

The pattern of the bacterial strains recovered in the three weeks' period from injury to healing paralleled, in general, that of the first three weeks of the full-thickness burn wounds under penicillin therapy (Chart 5; cf. Chart 1).

The differences noted are that the number of strains recovered throughout were fewer, that the increase in number of strains in the first two weeks is numerically less and that neither the streptococci nor the *Clostridia* increased at all in incidence. What increase there was in bacterial strains, therefore, is accounted for by the increase in gram-negative bacilli and diphtheroids and *B. subtilis*.

It is to be noted that although there was no significant change in incidence of the gram-negative bacilli in the wounds of partial-thickness in the patients under the sulfonamides, the same rapid increase in numbers as in the full-thickness wounds took place in the partial-thickness wounds in the first 14 days under penicillin.

(5) DISTRIBUTION OF FLORA ACCORDING TO BODY AREA

In order to see whether the quality of the bacterial contamination differs in various body areas, influenced perhaps by proximity to the mouth or anus, the flora encountered in wounds of the head and neck, upper, and lower extremities have been separately listed (Table I). Using both partial- and full-thickness wounds of patients receiving no chemotherapy as well as of those receiving penicillin or sulfadiazine, there are available for this analysis 35 wounds of the head and neck, 105 of the upper extremities and 65 of the lower extremities. To permit differentiation of the initial contamination from that occurring while in the hospital the flora found on the day of injury and that from the 1st to 14th days after injury have been separately considered.

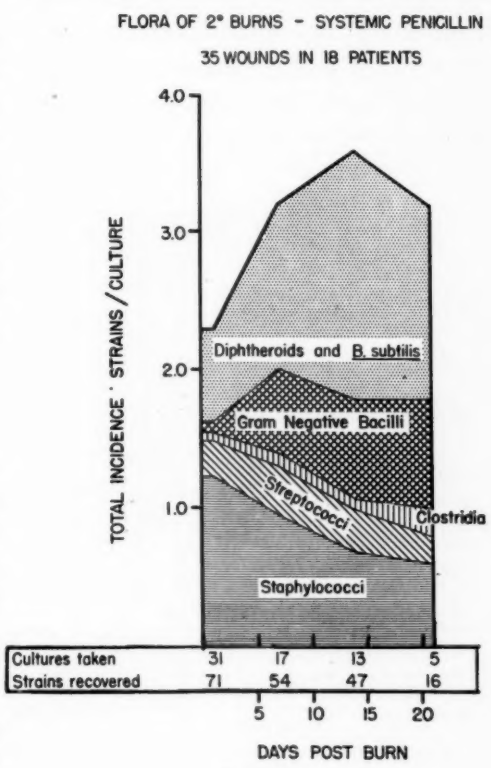


CHART 5

CHART 5.—The Bacterial Flora of Partial-thickness Burn Wounds in Patients Receiving Penicillin Therapy: Thirty-five wounds of 18 patients were followed from the day of injury to the 21st day or until healed. Cultures were by Swab technic. Systemic penicillin was started on the day of injury and continued throughout the period of observation.

From this cross-filling of the data it is apparent that wounds of the lower extremities were maximally contaminated at the time of entry to the hospital. Of all wounds these also showed the highest initial and subsequent *Clostridial* and *gamma* streptococcal infestation. Wounds of the head and neck showed the lowest initial contamination. Wounds both of the head and neck and of the upper extremities partook of the over-all increase in number and varieties

of bacterial strains in the first two weeks but the strains were throughout more abundant in the wounds of the upper extremities. In the wounds of the head and neck, *Clostridia* were least often encountered, but one-third as often as in the leg wounds, and, again in contrast to the legs, no *gamma* streptococci were recovered.

Of the other streptococci, not a single *beta* streptococcus was recovered from the 54 cultures taken on the day of injury from wounds of the upper extremities, yet the occurrence and distribution of the *alpha* streptococci in all wounds and at all times were remarkably even; it was the most common streptococcus found.

TABLE I

COMPARATIVE FLORAS OF BURN WOUNDS OF DIFFERENT BODY AREAS
PARTIAL AND FULL-THICKNESS BURN WOUNDS
SULFADIAZINE OR PENICILLIN

Body Area	Head and Neck		Upper Extremities		Lower Extremities	
Number of wounds	35		105		65	
Day postburn	0	1–14	0	1–14	0	1–14
Cultures taken	12	54	54	139	41	102
Strains recovered	39	202	182	563	167	423
Incidence of strains (strains per culture)	3.2	3.7	3:4	4:1	4.2	4.2
	Percentage of Strains Isolated					
Diphtheroids and *B. subtilis*	35.9	37.6	39.1	36.8	36.5	34.0
Gram-negative bacilli	2.6	9.9	3.3	6.9	3.0	9.6
Clostridia	5.1	3.0	13.7	6.2	15.6	9.6
Streptococci:	15.3	14.8	12.6	17.8	12.6	20.2
Beta streptococci	2.6	4.0	0	3.0	1.8	3.1
Alpha streptococci	12.7	10.8	12.6	12.3	10.2	12.8
Gamma streptococci	0	0	0	2.5	0.6	4.3
Staphylococci:	41.1	34.7	31.3	32.3	32.3	26.6
Staph. aureus, Coag. +	2.6	20.3	3.3	17.4	3.6	12.1
Staph. albus, Coag. +	2.6	1.5	0.6	2.1	1.8	4.1
Staph. aureus, Coag. −	7.7	1.0	2.2	2.1	6.6	0.9
Staph. albus, Coag. −	28.2	11.9	25.2	10.7	20.3	9.5

Contrary to the slow decline in number of strains of staphylococci found generally, including the wounds of head and neck and legs, there was no decrease in number in the wounds of the upper extremities. The increase in gram-negative bacilli is more prominent in wounds of the head and neck and lower extremities than in those of the arms.

CONCLUSIONS

In a study of the effectiveness of systemic chemotherapy in the control of the infection of burns, the appearance and subsidence of invasive infection has been observed and a comparison of the bacterial flora of burn wounds made in patients receiving either penicillin or sulfadiazine. These chemotherapeutic agents were found to exert a limited but different control of the organisms in the wound.

Statistical analysis of the influence of chemotherapy upon invasive infection has not been possible because of the difficulty in judging objectively its presence in the burn wound. The effectiveness of penicillin and sulfadiazine on invasive infection remains, therefore, a clinical impression. It will be discussed at the end of the fourth part.

The study of the bacterial flora of the burn wounds is objective, detailed and subject to analysis. Neither sulfadiazine nor penicillin obliterated bacteria in a burn wound. The lesser number of bacterial strains recovered in wounds of partial-thickness compared with those of full-thickness, under either penicillin or sulfadiazine, suggests that there are unknown influences in the full-thickness wound, presumably related to the amount of dead tissue, limiting the action of these chemotherapeutic agents.

In patients receiving penicillin the number of bacterial strains recovered from the wounds increased rapidly in the first two weeks after injury; from the wounds of full-thickness destruction the number of strains subsequently recovered was slightly higher than in the comparable wounds of patients receiving sulfadiazine.

Penicillin exerted a more decisive brake than sulfadiazine on the growth of staphylococci. In the wounds of patients treated with penicillin from the time of injury, the number of strains of staphylococci slowly declined, while in those of patients receiving sulfadiazine the number of strains did not vary. In patients in whom penicillin therapy was delayed the number of strains of staphylococci before therapy was the highest observed; following onset of penicillin there was a prompt fall in the number recoverable.

There was an abrupt rise in the number of strains of gram-negative bacilli recovered from the wounds of patients receiving penicillin in the 2nd week of therapy. That this rise did not appear before onset of therapy in patients in whom the penicillin was delayed and did appear in the same time sequence following administration of penicillin and that this early rise was not observed in the sulfadiazine-treated patients, suggests that the penicillin was responsible for this profusion of gram-negative organisms.

The number of strains of streptococci was held lower by sulfadiazine than by penicillin. The nature of this control is described in detail in the fourth part.

The wounds of certain body areas showed different bacterial contamination. Wounds of the lower extremity on the day of injury already showed the maximal number and variety of strains encountered. The *Clostridia* and the *gamma* streptococcus, organisms commonly found in the colon, were more often found in these wounds than in those of other areas.

From wounds of the head and neck the least number of bacterial strains was recovered on the day of injury. The number from the wounds of the upper extremity lay midway between that of the head and neck and of the lower extremity. No *gamma* streptococci were found initially in the wounds of either head and neck or upper extremities and no *beta* streptococci in the wounds of the latter area.

In seeking the source of the bacteria contaminating burn wounds it should be pointed out that the flora found in the three wound areas on the day of injury are reminiscent of the resident flora expected. Fecal organisms should be more prevalent on skin near the anus. Skin of the hands has been shown by Colebrook and Maxted,[17] to have the power to rid itself of the *beta* streptococcus. It is tempting, therefore, to assume that the organisms found

are the resident flora which survive the burn. If this were true the greater number of strains of organisms should have been found in the less deeply burned wounds rather than in those of full-thickness. This not being so, the resident flora may have been killed by the burn and the contaminating bacteria may have been transported from a location close to the wound, such as the clothing, or from the original source, as the anus itself.

Even if the quality of the flora found on the day of injury tends to exclude dust or other chance contamination as the principal source of the original bacteria, the inadvertent transfer of organisms from the wound of one patient to that of another, which has been observed in the hospital in spite of strict precautions, points-up the necessity of stringent regulations for the care of burn patients.

REFERENCES

1 Hooker, Donald H., and Lam, Conrad R.: Absorption of Sulfanilamide from Burned Surfaces. Surgery, **9**, 534, 1941.

2 Pickrell, Kenneth L.: A New Treatment for Burns: Preliminary Report. Bull. Johns Hopkins Hosp., **69**, 217, 1941.

3 Gurd, Fraser B., Ackman, Douglas, Gerrie, John W., and Pritchard, J. E.: A Practical Concept for the Treatment of Major and Minor Burns. ANNALS OF SURGERY, **116**, 641, 1942.

4 Evans, Everett I., Hoover, M. J., and James, G. Watson, III: The Absorption of Sulfonamides from the Burn Surface. Surg. Gynec. Obst., **80**, 297, 1945.

5 Cope, Oliver: The Management of the Cocoanut Grove Burns at the Massachusetts General Hospital. The Treatment of the Surface Burns. ANNALS OF SURGERY, **117**, 885, 1943.

6 Cope, Oliver: The Chemical Aspects of Burn Treatment. J. A. M. A., **125**, 536, 1944.

7 Cope, Oliver, Langohr, John L., Moore, Francis D., and Webster, Richard C., Jr.: Expeditious Care of Full-thickness Burn Wounds by Surgical Excision and Grafting. ANNALS OF SURGERY, **125**, 1, 1947.

8 Meleney, Frank L.: A Statistical Analysis of a Study of the Prevention of Infection in Soft-part Wounds, Compound Fractures, and Burns, with Special Reference to the Sulfonamides. Surg. Gynec. Obst., **80**, 263, 1945.

9 Colebrook, L., *et al.*: Studies of Burns and Scalds (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942–43). Medical Research Council, Special Report Series No. 249, London: His Majesty's Stationery Office, 1944.

10 Cruickshank, Robert: The Bacterial Infection of Burns. J. Path and Bact., **41**, 367, 1935.

11 Rosenthal, L.: Chromium-sulfuric Acid Method for Anaerobic Cultures. J. Bact., **34**, 317, 1937.

12 Mueller, J. H., and Miller, P. A.: A Modification of Rosenthal's Chromium-sulfuric Acid Method for Anaerobic Cultures. J. Bact., **41**, 301, 1941.

13 Owen, Cora R.: Acetic Acid Inhibition of Gram-negative Bacilli in Culture Media. J. Bact., **52**, 353, 1946.

14 Larson, W. P.: Personal Communication.

15 Spray, R. S.: Semisolid Media for Cultivation and Identification of the Sporulating Anaerobes. J. Bact., **32**, 135, 1936.

16 Lyons, Champ: The Management of the Cocoanut Grove Burns at the Massachusetts General Hospital: Problems of Infection and Chemotherapy. ANNALS OF SURGERY, **117**, 894, 1943.

17 Colebrook, L., and Maxted, W. R.: Antisepsis in Midwifery. J. Obst. and Gynec. Brit. Emp., **40**, 966, 1933.

(*Continue with Part II*)

PART II

THE DEVELOPMENT OF RESISTANCE TO PENICILLIN BY THE FLORA OF FULL-THICKNESS BURN WOUNDS IN PATIENTS TREATED WITH PENICILLIN SYSTEMICALLY

THE ENCOUNTERING of drug-resistant bacteria in patients during the course of sulfonamide therapy, the report of a comparable development of resistance of organisms to penicillin and of the power of bacteria to inhibit the action of penicillin, prompted the estimation, as an integral part of the study of the bacteriology of burn wounds, of the sensitivity and the development of resistance to penicillin and of the inhibition of penicillin by the bacterial flora. When this study was initiated in 1943 there was evidence that certain types of bacteria, normally sensitive to the sulfonamides, could develop an indifference or resistance to the drug.[1] Grown *in vitro* in media containing increasing concentrations of a sulfonamide, the metabolism of the organisms changed to the extent of becoming inured to the drug and growing without restraint. Such resistance was also believed to develop *in vivo*. Colebrook,[2] from the burn wounds of patients receiving sulfonamides, recovered first a sulfonamide-sensitive *beta* streptococcus, subsequently a drug-fast organism of the same strain, and reasonably suggested that the fastness had been induced.

When penicillin first became available to civilian Centers in this country, observations were available suggesting that similar development of drug resistance was to be expected during the course of penicillin therapy.[3, 4] Measurement of the development of resistance or loss of sensitivity should indicate not only the period during which the drug could be expected to be maximally effective but also whether the drug penetrated the burn slough, should the organisms in the slough retain their sensitivity.

Just as the bacteriostatic action of the sulfonamides had been found by several workers to be inhibited by breakdown products of bacteria and cells.[1] so that of penicillin had been reported thwarted by growth of nonsensitive organisms. Abraham and Chain[5] recorded, in 1940, that the gram-negative bacilli produced an enzyme-like substance which destroyed penicillin, and which they termed penicillinase. Because of the deterring influence which contaminating bacteria might exert through such inhibition, measurement of inhibition by those organisms commonly encountered in the flora of burn wounds was deemed prudent.

METHODS

A first part of the laboratory effort of this study was the development of methods for the measurement of penicillin sensitivity and inhibition. The first test of the bacterial sensitivity to penicillin (Introductory Test), useful as a step in the measurement of bacterial inhibition, proved unnecessarily cumbersome as a routine test and was supplanted by a simpler method (Routine Test).

Bacterial Sensitivity to Penicillin (Introductory Test).—The naturally-occurring penicillin sensitivity of a bacterium was determined by comparing its growth in a medium containing penicillin with that in a penicillin-free medium. Growth was judged by turbidity of the media. Five-cubic centimeter portions of nutrient broth containing 50, 25, 5, 1 and 0 units of penicillin per cubic centimeter were inoculated with 0.1 cc. of an 18-hour broth culture of the organism to be tested and incubated for 18 hours at 37° C. Any strain whose growth was not inhibited by penicillin in the concentrations above five units per cc. was considered to be resistant to penicillin. Any strain whose growth was inhibited by concentrations of five, or less, units per cc. was considered sensitive.

Bacterial Inhibition of Penicillin.—To decide whether a test organism had the power to inhibit the antibacterial action of penicillin, small disks of sterile filter paper which had been dipped into the inoculated broth tubes containing none or varying concentrations of penicillin were laid upon the surface of blood agar plates previously inoculated with a staphylococcus of known high sensitivity to penicillin. (No attempt was made to destroy the test strain growing in the broth tubes.) After incubation at 37° C. for 18 hours the plates were examined for zones of inhibition of the growth of the staphylococcus around the disks. An organism was considered to be a penicillin-inhibitor if the growth of the known staphylococcus on the plate was not inhibited and if the test fluid had come from a tube which had contained five units, or more, of penicillin per cubic centimeter.

Bacterial Sensitivity to Penicillin (Routine Test).—All gram-positive organisms isolated from the patients on penicillin, except diphtheroids and aerobic sporulating bacilli, were tested for sensitivity to penicillin. A five per cent horse blood agar "pour" plate was made with 0.05–0.1 cc. of an 18-hour liquid culture of the organism to be tested and allowed to harden. Filter paper disks, cut with an ordinary paper punch from thin, "rapid filter" type paper and sterilized by dry heat, were dipped into solutions of 50, 25, 5 and 1 units per cc. of penicillin in isotonic saline, drained on sterile gauze sponges, and laid on the surface of appropriately marked segments of the plate. After 18-hour incubation at 37° C., aerobically or anaerobically according to the requirements of the organism under test, the plates were examined for zones of inhibition of growth of the test organism by the penicillin. Strains not inhibited by concentrations of penicillin above five units per cc. were considered resistant and are classified as such in the charts.

OBSERVATIONS

1. *Natural Ability of Wound Bacteria to Resist and Inhibit Penicillin.*—The penicillin resistance and inhibitory power of 207 bacterial strains were studied. The strains were either isolated from patients with various surgical infections or found as contaminants in the laboratory media. Since none of the patients from whom the bacteria were isolated had received penicillin and, indeed, since no patient had been studied up to this time who had re-

ceived penicillin, it was deemed that none of the organisms could have an artificially-induced reaction to penicillin. The findings are summarized in Table II.

Of the 16 strains of streptococci tested, only one (6 per cent) was found to be resistant to penicillin. This was a *beta hemolytic Streptococcus,* Group A-Lancefield, which was not inhibited by concentrations of 50 units of penicillin per cc. of broth and which showed no evidence of inhibitory action against penicillin. (This native resistance of a *beta hemolytic Streptococcus* has not otherwise been encountered in our experience, nor have we found it mentioned in the literature.) One strain (6 per cent), a sensitive *gamma nonhemolytic Streptococcus,* was found to be inhibitory to penicillin.

Of the staphylococci, 8 of 118 strains (7 per cent) were resistant to penicillin; 8 (7 per cent), 6 of the 8 resistant and 2 sensitive strains, inhibited the drug. Five (16 per cent) of the 32 coagulase-positive and four (5 per cent) of the 86 coagulase-negative strains were resistant, a three-fold greater incidence of resistance among the more virulent staphylococci. Of the coagulase-positive strains, none of the 27 sensitive and three of the five resistant organisms (60 per cent) were inhibitory; of the coagulase-negative, two of the 82 sensitive (3 per cent) and 100 per cent of the five resistant strains were inhibitory. Of the 45 *Staph. aureus,* no sensitive and four of the six resistant (67 per cent), and of 73 *Staph. albus* the two resistant and two of the 71 sensitive strains (3 per cent) inhibited the penicillin. Thus, penicillin inhibition by sensitive strains of staphylococci was found only in 2 coagulase-negative *Staph. albus,* both recovered as contaminants on laboratory media; natively resistant strains do not invariably produce penicillin inhibitors detectable by this method.

Nine of 30 diphtheroids (30 per cent) were resistant to penicillin; all of these and three of the 31 sensitive strains (14 per cent) inhibited the drug's action.

Twenty-two of 34 aerobic spore-formers (*B. subtilis*) (65 per cent) were resistant to penicillin and 27 (80 per cent) inhibited its action. One resistant strain did not inhibit, but six (50 per cent) of the sensitive strains did so.

Only nine strains of gram-negative bacilli of the *coli-pyocyaneus-proteus* group were tested at this time. All were resistant to penicillin, and all but the two strains of *B. proteus* were inhibitory. Since that time we have tested four more strains of *B. proteus* and found them to be inhibitory; these were, however, isolated from patients who were receiving the drug.

In summary, there is no absolute correlation between the organisms resistant to the bacteriostatic action of penicillin and those capable of inactivating or inhibiting this agent.

2. Resistance to Penicillin of the Flora of Full-thickness Burn Wounds in Patients Treated with Penicillin.—The initial occurrence of resistance to penicillin and its subsequent development was followed in the gram-positive strains recovered from the 80 wounds of the 28 patients with full-thickness burn wounds treated with penicillin from the day of injury. (The wounds and

TABLE II

RESISTANCE TO, AND INHIBITION OF, PENICILLIN BY ORGANISMS NOT PREVIOUSLY EXPOSED TO THE DRUG

Organism	Number of Strains Tested	Penicillin-sensitive Per Cent	Penicillin-resistant Per Cent	Penicillin-inhibiting Per Cent	Penicillin-noninhibiting Per Cent	Penicillin-sensitive			Penicillin-resistant		
						Total Number	Inhibiting Per Cent	Non-inhibiting Per Cent	Total Number	Inhibiting Per Cent	Non-inhibiting Per Cent
Streptococci	16	94	6	6	94	15	7	93	1	0	100
Beta	8	88	12	0	100	7	0	100	1	0	100
Alpha	6	100	0	0	100	6	0	100	0	..	..
Gamma	2	100	0	50	50	2	50	50	0	..	..
Staphylococci	118	93	7	7	93	110	2	98	8	75	25
Coag +	32	84	16	9	91	27	0	100	5	60	40
Coag 0	86	95	5	6	94	82	3	97	5	100	0
Staph. aureus											
Coag +	30	83	17	10	90	25	0	100	5	60	40
Coag 0	15	93	7	7	93	14	0	100	1	100	0
Staph. albus											
Coag +	2	100	0	0	100	2	0	100	0	..	..
Coag 0	71	97	3	6	94	69	3	97	2	100	0
Diphtheroids	30	70	30	47	53	21	14	86	9	100	0
Aerobic spore-formers	34	35	65	79	21	12	50	50	22	96	4
Gram-negative bacilli	9	0	100	78	22	0	..	..	9	78	22
Total	207										

patients are the same as those studied under section one (Chart I) of Part I.) The sensitivity of a few strains, mainly *Clostridia,* which were difficult to grow and isolate, was not observed. The penicillin sensitivity of diphtheroids, *B. subtilis,* and gram-negative bacilli was, also, not observed. It was taken for granted from the previous studies that the diphtheroids and *B. subtilis* groups were 50 per cent penicillin-resistant, and the gram-negative

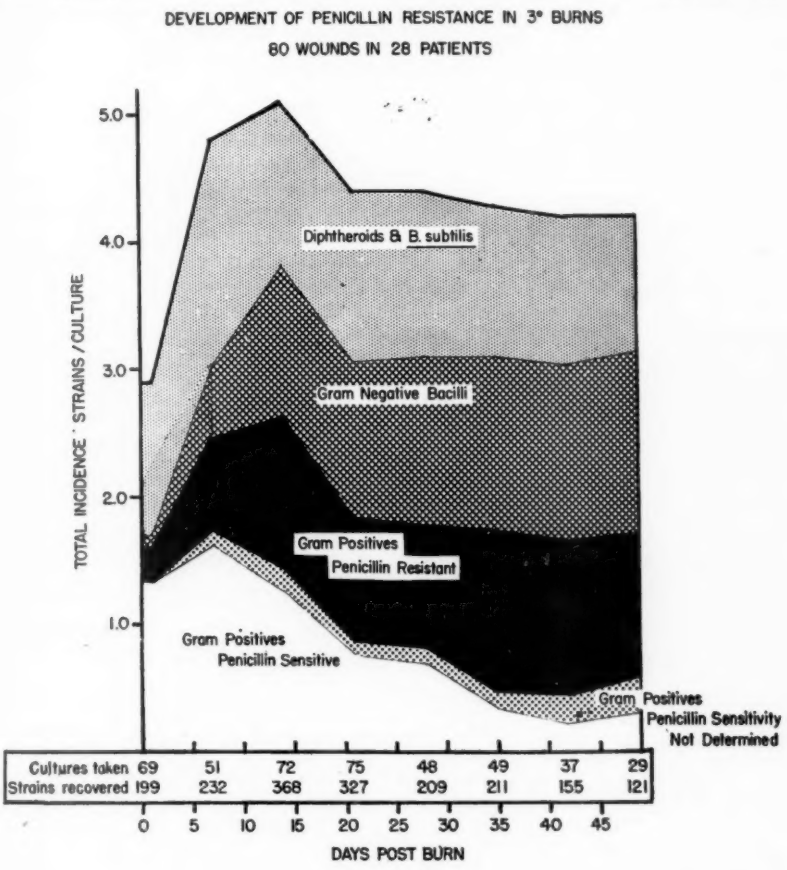


CHART 6

CHART 6.—The Occurrence of Penicillin Resistance in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: Eighty wounds of 28 patients (cf. Chart 1 of Part I) were followed from the day of injury throughout a course of penicillin therapy. All gram-positive organisms, except diphtheroids and aerobic spore-formers (*B. subtilis*), were tested for sensitivity to penicillin. Strains not inhibited by concentrations of penicillin of 25, or more, units per cubic centimeter were considered penicillin-resistant; strains inhibited by 5, or less, units per cubic centimeter were considered penicillin-sensitive.

bacilli 100 per cent resistant. No study of the inhibitory power of any of the organisms was undertaken although the experience with the four *B. proteus* strains quoted in the previous section suggests that this might have been interesting.

Approximately 30 per cent of the bacterial strains recovered on the day of injury by swab culture were found to be penicillin-resistant (Chart 6). This 30 per cent was made up of one-half of the diphtheroids and *subtilis*, all of the gram-negative bacilli and 20 per cent of the gram-positive organisms, including streptococci, staphylococci and *Clostridia*. During the course of penicillin therapy, after an increase of penicillin-sensitive strains in the first seven days, there was a progressive disappearance until the 42nd day when

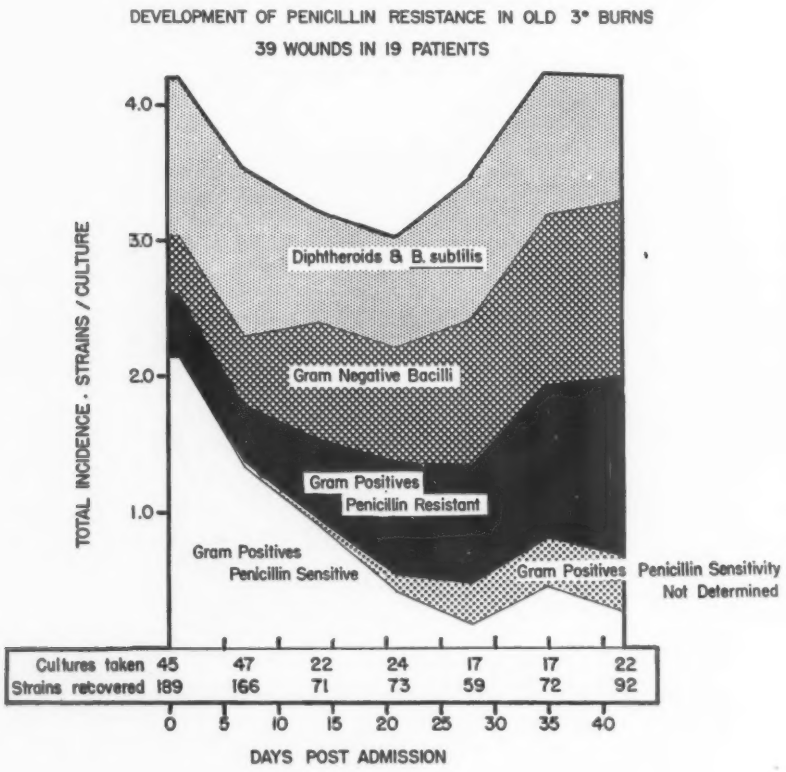


CHART 7

CHART 7.—The Occurrence of Penicillin Resistance in the Flora of Full-thickness Burn Wounds of Patients whose Hospital Admission and Penicillin Therapy were Delayed: Thirty-nine wounds of 19 patients (cf. Chart 2 of Part I) were followed from the day of admission throughout a course of penicillin therapy. Penicillin resistance of the flora was ganged in this group of patients as described in the legend of Chart 6.

the minimum number was reached. During the first seven days there was also an increase in number of resistant gram-positive organisms. After the 7th day, as the sensitive strains disappeared they were replaced by resistant strains in approximately the same proportion. By the 14th day after injury the number of resistant gram-positive strains was quadrupled, and by the 21st day there was only half the original number of gram-positive sensitive strains left. By the 42nd day only 10 per cent of all the gram-positive strains re-

covered were sensitive. In addition to these changes in the gram-positive flora, in the 42 days there had been an eleven-fold increase in the gram-negative strains. Thus, in contrast to the day of injury, when 70 per cent of all of the strains had been sensitive, on the 42nd day not more than 19 per cent were sensitive *in vitro* to penicillin.

The initial occurrence and subsequent development of resistance to penicillin was also studied in the bacteria recovered from the wounds of those patients with full-thickness burn wounds in whom the onset of penicillin therapy was delayed. The gram-positive flora of the 39 wounds of the 19 patients was studied (Chart 7; cf. Chart 2 of Part I).

The trends of decreasing sensitivity and increasing resistance are the same as in those wounds of the patients in whom penicillin was started on the day of injury. The minimum number of sensitive strains is reached earlier, however, at the 28th instead of the 42nd day.

CONCLUSIONS

The progressive increase in numbers of bacteria which are resistant to penicillin and which normally are predominantly sensitive, the concomitant decline in numbers of penicillin-sensitive bacteria and the early overgrowth of bacteria commonly inhibitory of penicillin action in the full-thickness burn wounds of patients receiving penicillin therapy, suggest that the most effective therapeutic period of the drug is sharply limited to the first three weeks. By the 5th week of penicillin therapy the wound is a quagmire of resistant and inhibiting bacterial organisms over which penicillin exerts but little control. Though both drug resistance and inhibition are measured *in vitro*, the parallelism of the observed resistance to, and inhibition of, penicillin by the bacteria recovered from the burn wound and the clinical impression of the limited effectiveness of penicillin in controlling infection in the later weeks of therapy indicate that the tests are significant.

REFERENCES

[1] Janeway, Charles A.: Medical Progress: The Sulfonamides: I. Their Mode of Action and Pharmacology. New England J. Med., **227**, 989, 1942.

[2] Colebrook, L., *et al.*: Studies of Burns and Scalds (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942–43). Medical Research Council, Special Report Series No. 249, London: His Majesty's Stationery Office, 1944.

[3] Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin. Lancet, **2**, 177, 1941.

[4] Lyons, Champ: Penicillin Therapy of Surgical Infections in the U. S. Army. J. A. M. A., **123**, 1007, 1943.

[5] Abraham, E. P., and Chain, E.: An Enzyme from Bacteria Able to Destroy Penicillin. Nature, London, **146**, 837, 1940.

(*Continue with Part III*)

PART III

THE INCIDENCE, VIRULENCE AND RESISTANCE TO PENICILLIN OF THE STAPHYLOCOCCUS IN BURN WOUNDS OF PATIENTS TREATED WITH PENICILLIN OR SULFONAMIDES

The Significance of Staphylococcal Immunity to the Healing of the Wounds Infected with the Staphylococcus

THE POSSIBLY injurious rôle of the staphylococcus in burn wounds has received but scant attention, overshadowed, as it has been, by the flamboyant infection of the streptococcus. With the exception of the tetanus organism, known in a burn wound to give rise occasionally to clinical tetanus, students of infection in burns, traditionally, have been engrossed with the streptococcus. The vital dyes (gentian violet, brilliant green and acriflavine) were introduced by Aldrich,[1] with the objective of controlling the streptococcus. Investigating the effect of the sulfonamides in burns during 1942 and 1943, Colebrook, and his collaborators,[2] although recounting the presence of the staphylococcus and other organisms, have continued to center their thoughts on the streptococcus. They state: "Staphylococci have given rise to comparatively little acute or serious sepsis, and their influence upon the rate of healing in burns has been much less evident than that of hemolytic streptococci. Unlike the streptococci, too, they have seldom, if ever, been responsible for the failure of grafting operations."

The advent of the sulfonamides, the first relatively nontoxic agent achieving control over the streptococcus, and recent knowledge of the virulence and immunologic reactions of the staphylococci have set the stage for the study of the staphylococcal infection of burn wounds. Lyons,[3] in his bacteriologic study of the nine victims of the Cocoanut Grove disaster with full-thickness burns, who were treated with sulfadiazine, found a singular discrepancy in the incidence in the wounds of the streptococci and that of the staphylococci. The *beta* streptococcus was recovered from 30 per cent, or less, of the wounds and had disappeared by the 6th week. The *alpha* streptococcus, present in the 1st week in 60 per cent of the wounds, had disappeared by the 5th week. The *gamma* type was recovered even less often than the *beta*. The staphylococcus, found in every wound, persisted in the virulent form in more than 80 per cent of the wounds throughout the nine weeks of observation. Such a disparity in incidence between the streptococcus and staphylococcus, presumably due to the suppression of the streptococcus by the sulfadiazine, offered a means of judging the destructiveness of the staphylococcus in the wounds of patients to be treated with sulfadiazine. The disparity also offered the control needed to evaluate the effectiveness of penicillin against both streptococcus and staphylococcus.

Also, indicating a more extended study of the staphylococcus in burn wounds, was the recent recognition of the varying pathogenicity of its types and of an immunologic response to its presence. As the result of experience

with surgical infections other than burns, such as the carbuncle, in which the staphylococcus was the sole organism recovered, it was generally agreed[4-9] that the clinical virulence of the infection varied with the metabolic type of the staphylococcus. The yellow staphylococcus, *Staph. aureus,* is more virulent than the white, *Staph. albus;* the property of coagulating human plasma protein also denotes greater virulence. Lyons[10] has reported the presence in the blood serum of rabbits injected with heat-killed staphylococci of agglutinins specific for the strain of staphylococcus. By observing the color and coagulating property of the staphylococci found, by search for specific agglutinins and by quantitation of certain nonspecific globulins in the blood serum of the burned patients, it was believed objective data could be obtained regarding the virulence of the infection and the degree of immune response.

METHODS

In addition to the bacteriologic methods recounted in the first two parts and the usual chemical methods for estimating plasma protein, the following methods have been used:

The euglobulin and pseudoglobulin levels of the blood serum were determined by the sodium sulfate protein fractionation method of Howe.[11]

Specific agglutinins to the staphylococcus recovered from the wound were tested for in the blood serum of the patient by the macroscopic slide-agglutination technic of Lyons.[10]

Autogenous staphylococcal vaccine was prepared according to Lyons.[10]

OBSERVATIONS

Incidence.—In every full-thickness burn wound the presence of a staphylococcus is to be expected. From each culture taken on the day of injury, 1.1 strains of staphylococci were recovered from the wounds of the patients subsequently treated with penicillin (Chart 9), and 1.2 strains from those of the patients subsequently treated with sulfadiazine (Chart 8).* As pointed out in the first part of this study on bacteriology, during the course of systemic therapy with penicillin the over-all incidence of the staphylococcus in the full-thickness burn wound slowly decreased, while under sulfadiazine there was no change. When the individual wounds are examined, approximately one-third of the wounds under either drug lost their staphylococci before healing had taken place. Of the 46 wounds in patients treated with sulfadiazine, 33 per cent lost their staphylococci. Of the 80 wounds in patients receiving penicillin, 37 per cent lost theirs. This apparent discrepancy with the over-all incidence is explained by the fact that certain patients under

* A slightly higher incidence of the staphylococcus in the 13 cultures made by means of débrided tissue in the cases subsequently treated by sulfonamides might appear to be due to the method of culturing. In the second-degree burns, however, the different methods of culturing yielded identical numbers of staphylococcal strains per culture (Charts 3 and 4 of Part I. The slight difference in the full-thickness burn wound is probably not statistically significant since but 13 cultures were taken in the cases subsequently treated by sulfonamides.

sulfadiazine having multiple wounds lost all staphylococci, whereas other patients acquired two, and even three, different staphylococci per wound, and lost none.

A comparable disappearance of staphylococci from wounds of patients

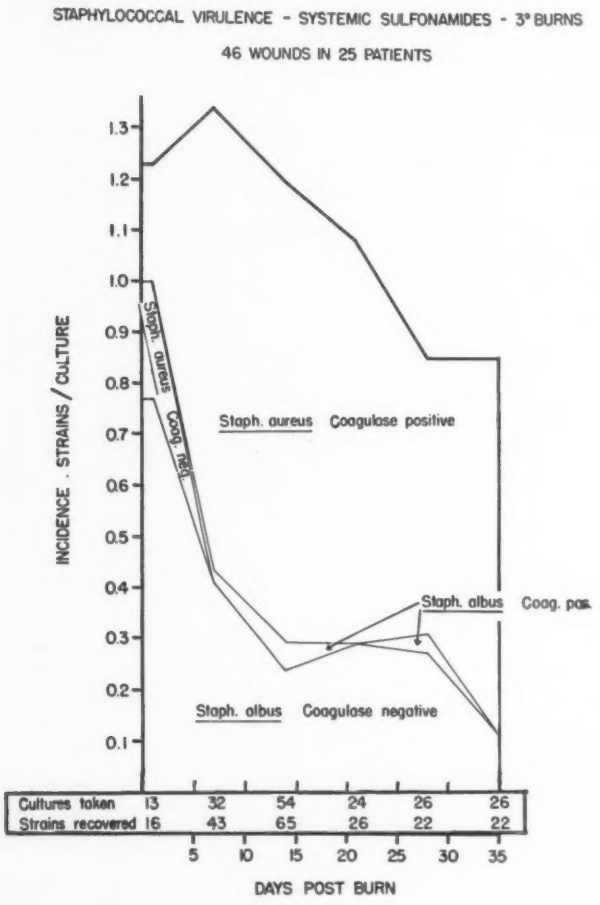


CHART 8

CHART 8.—The Incidence and Virulence of the Staphylococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Sulfonamide Therapy: The staphylococci isolated from 46 wounds of 25 patients (cf. Chart 3 of Part I) were tested for chromogenesis and the power to coagulate human plasma protein. (Hemolysis was noted but is not recorded.) Virulence was graded on the basis of these two attributes; thus, the *Staph. aureus*, coagulase-positive, is fully virulent, the *Staph. albus*, coagulase-negative, avirulent.

under no chemotherapy was observed in the few patients available for study during the course of these observations who did not receive one, or another, chemotherapeutic agent. No common factor in the condition of the wounds

of the groups of patients, such as the presence of slough or the local treatment applied, were discerned which could account for the disappearance of the staphylococci.

Virulence.—The number and proportion of virulent strains of the staphylococci increased in full-thickness burn wounds with the passage of time under either sulfadiazine or penicillin therapy. Of the staphylococci recovered on the day of injury 75 per cent were of the least virulent form, *Staph. albus,* coagulase-negative, and but 15 per cent of the fully virulent, *Staph. aureus,* coagulase-positive. The two intermediary groups made up the remaining 10 per cent.

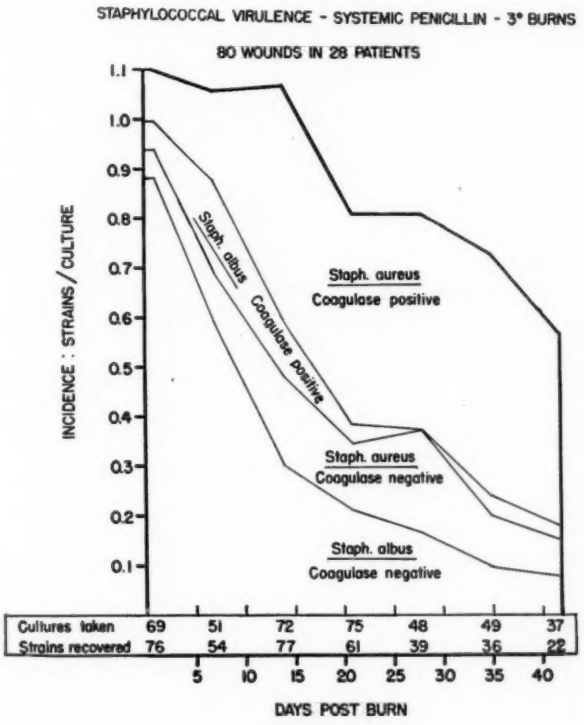


CHART 9

CHART 9.—The Incidence and Virulence of the Staphylococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: The staphylococci isolated from 80 wounds of 28 patients (cf. Charts 1 and 6 of Parts I and II) were tested for chromogenesis and the power to coagulate plasma and the virulence graded as recounted in legend of Chart 8.

During the course of the first six weeks there was a progressive loss of the avirulent and a steady increase of the virulent forms, until by the 6th week the relation of *"albus"* to *"aureus"* was reversed. At this time, in the penicillin-treated cases the *"albus,"* coagulase-negative, accounted for less than 20 per cent of the strains recovered, and the *"aureus"* for 70 per cent;

in the sulfadiazine-treated cases, 85 per cent of the staphylococci were of the *aureus* form. Even when the decrease in number of total staphylococcal strains under penicillin is taken into account, there was, after six weeks of therapy with either drug, a greater number of virulent strains recoverable per culture which were fully virulent than there had been on the day of injury.

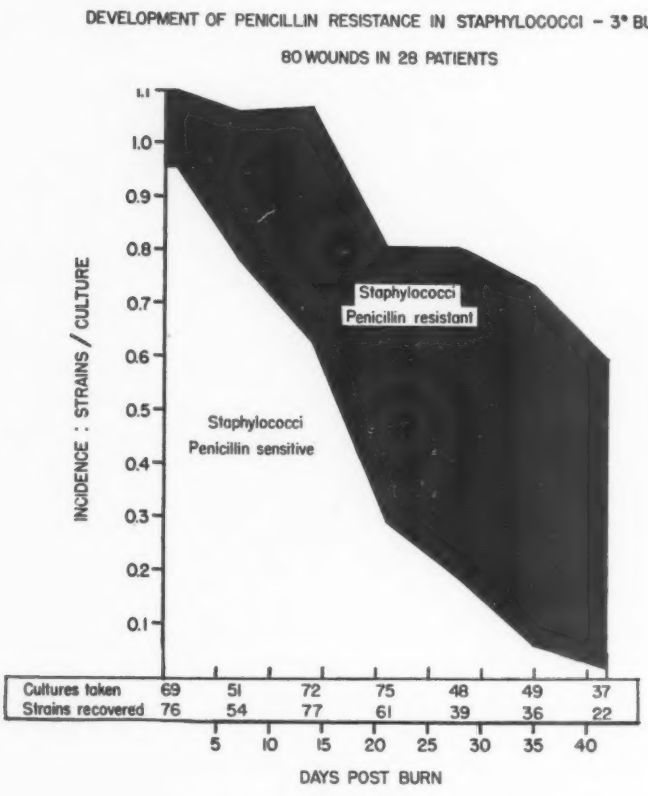


CHART 10

CHART 10.—The Penicillin Resistance of the Staphylococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: The staphylococci were isolated from 80 wounds of 28 patients (same group as in Chart 9; cf. Charts 1 and 6 of Parts I and II).

The *Staph. aureus,* coagulase-negative, and *Staph. albus,* coagulase-positive, the intermediary types, at any one time made up but a small proportion of the total staphylococcal strains; their number was almost negligible during the course of sulfonamide therapy, while their slightly greater incidence under penicillin is probably statistically significant.

Penicillin Resistance.—Even more striking than the changes in virulence of the staphylococcus recovered from full-thickness burn wounds, with the passage of time, is the development in these organisms of penicillin resistance. In the burn patients subsequently treated with penicillin but 14 per cent of the

strains of staphylococci were resistant on the day of injury and before onset of therapy. At the end of six weeks of penicillin treatment more than 90 per cent of the staphylococci recovered were resistant to the drug (Chart 10). All four types of the staphylococci developed resistance, but, apparently, not quite to the same degree (Chart 11). The fully virulent types by the 6th week were all resistant. Only the most avirulent form, *Staph. albus,* coagulase-negative, had

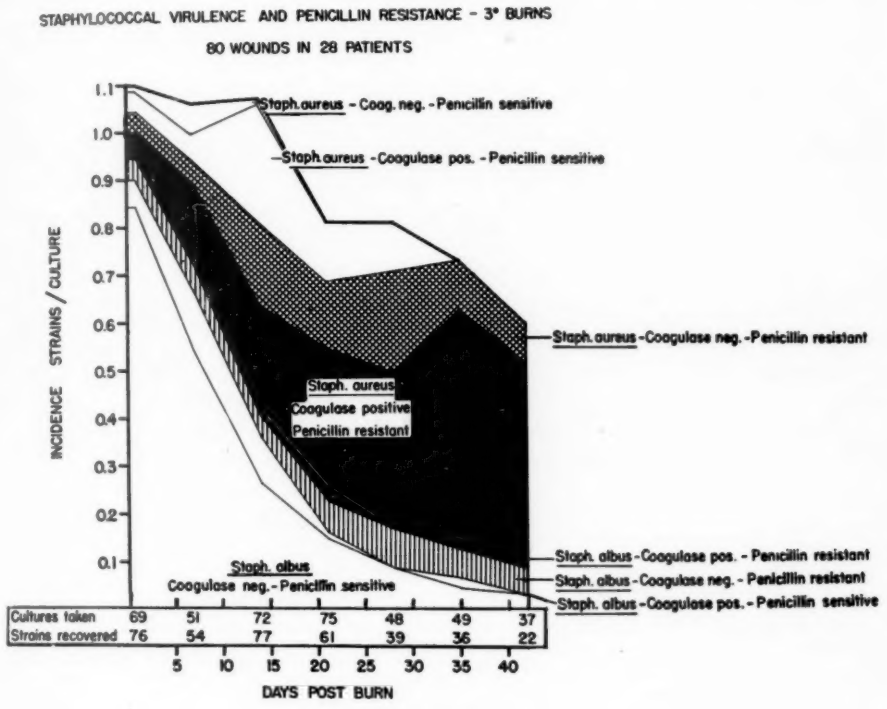

STAPHYLOCOCCAL VIRULENCE AND PENICILLIN RESISTANCE - 3° BURNS
80 WOUNDS IN 28 PATIENTS
INCIDENCE STRAINS / CULTURE
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Staph.aureus - Coag. neg. - Penicillin sensitive
Staph.aureus - Coagulase pos. - Penicillin sensitive
Staph.aureus - Coagulase neg. - Penicillin resistant
Staph. aureus
Coagulase positive
Penicillin resistant
Staph. albus
Coagulase neg. - Penicillin sensitive
Staph. albus - Coagulase pos. - Penicillin resistant
Staph. albus - Coagulase neg. - Penicillin resistant
Staph. albus - Coagulase pos. - Penicillin sensitive
Cultures taken 69 51 72 75 48 49 37
Strains recovered 76 54 77 61 39 36 22
5 10 15 20 25 30 35 40
DAYS POST BURN

CHART 11

CHART 11.—The Virulence and Penicillin Resistance of Staphylococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: This is a composite of Charts 8 and 9.

a significant number of penicillin-sensitive organisms during the 5th and 6th weeks of treatment.

Evidence was obtained of two types of acquired resistance to penicillin. The *in vivo*-acquired resistance may be permanent. The burn wound of one patient (Case 188), and the donor site of another (Case 137), both of which were infected originally with a penicillin-sensitive staphylococcus, during the course of penicillin therapy, yielded a resistant organism in place of the sensitive one. After two and 15 weeks of therapy, no further penicillin was administered. Two and one-half and three months after cessation, the staphylococcus recovered from each was still resistant. From the burn wounds of a third patient (Case 168) a penicillin-resistant staphylococcus was recovered three months after cessation of therapy. It is possible in this 3rd

patient that the staphylococcus was resistant before onset of therapy, since she had been treated with penicillin in another hospital before coming here, and no culture had been taken prior to onset of the therapy. The staphylococcus recovered from all three patients was of the fully-virulent type.

The *in vitro*-acquired resistance, which we have succeeded in producing, on the other hand, has proved transient. Penicillin resistance was induced

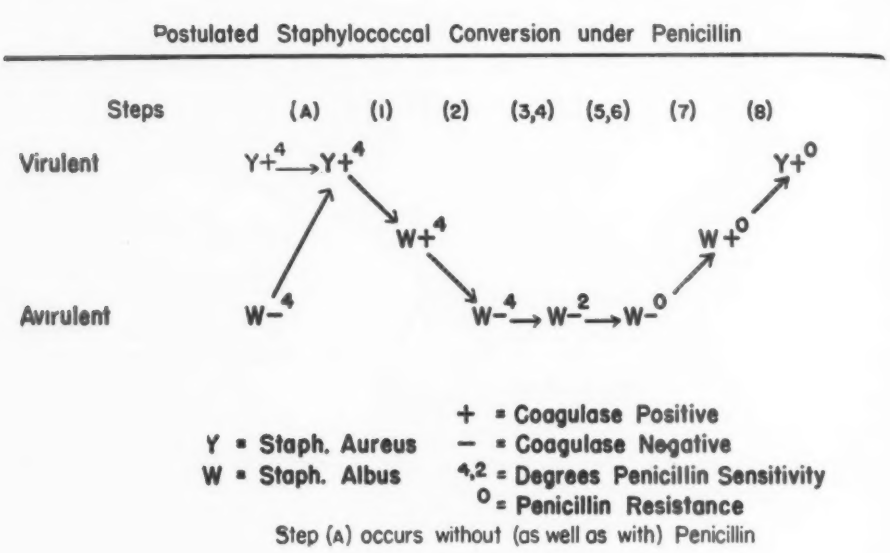


CHART 12

CHART 12.—Postulated Metabolic Mutation of the Staphylococci in the Wounds of Patients Receiving Penicillin Therapy: The frequently observed disappearance of avirulent forms of staphylococci and the appearance of virulent forms in the initial days after injury in patients receiving no chemotherapy or sulfadiazine has suggested a mutation from avirulent to virulent form. A similar change has been noted in the staphylococci recovered from patients treated with penicillin. During the succeeding two weeks of penicillin therapy avirulent forms are again found; such a reappearance has not been encountered in sulfonamide-treated patients or in those receiving no chemotherapy. After the 3rd week of penicillin therapy, when penicillin-resistant strains predominate, virtually all strains recovered are fully virulent. It is postulated that an initial effect of penicillin on staphylococci is a reduction of virulence but that if the staphylococcus survives by developing resistance, full virulence is regained.

in sensitive staphylococci by repeated cultures in media containing increasing concentrations of penicillin. This induced resistance was quickly dissipated by culturing the organisms in penicillin-free media. Only the *Staph. aureus,* coagulase-positive type, was used in these experiments. Spink, *et al.*,[12] have reported comparable findings.

Mutation Theory.—The gradual replacement of the avirulent by the virulent form of the staphylococcus in all burn wounds (Charts 8 and 9) and the frequency with which a change in form has been seen in wounds in which a single staphylococcal strain has been recovered at any one time, point strongly to a mutation of the staphylococcus. Such a mutation from the *Staph. albus*

to *Staph. aureus,* and from coagulase-negative to coagulase-positive has been previously postulated.[13-15] With the advent of penicillin, evidence has been obtained which carries the concept of the mutation two steps further (Chart 12). The first change of the penicillin-sensitive avirulent white staphylococcus is to a virulent yellow staphylococcus, still penicillin-sensitive. This step is the previously postulated mutation and, apparently, takes place whether the patient is on penicillin or not. In the patients under systemic penicillin therapy, the next change appears to be a reversion to a white form, with loss of coagulating power but still sensitive to penicillin. If the organism does not disappear and chemotherapy is continued, resistance to the drug develops. When the resistance is fully developed there is a second and final reversion to the virulent form.

Proteolysis.—During the course of penicillin therapy the wounds of nine of the patients with full-thickness burns developed a superficial dissolution which we had never previously seen and which was associated with a penicillin-resistant *Staph. aureus* and a *B. proteus.* The wound is characteristic in appearance, stubborn in therapy, and has been termed "proteolytic" because of its salient character. Such proteolytic wounds have not been encountered until after three weeks of penicillin therapy. There is a superficial liquefaction of epidermis and derma unaccompanied by any deep or subcutaneous inflammatory reaction. The margins of the wound, or of grafts previously placed upon the wound, melt away, leaving cadaveric-appearing, uninflamed yellow fat. The veins of the subcutaneous plexus may lie exposed on the surface of the fat, apparently intact, giving the wound its cadaveric look. There is little bleeding from the wound with change of dressing, and no granulations or fibrous tissue proliferation; little edema is visible. The wounds may lie, weeks long, in such an inactive state. After final epithelial closure, a late, and prolonged, deep inflammatory process is common with tenderness persisting as long as six months, and eventual profuse keloid formation.

In all of the proteolytic wounds of the nine patients, a penicillin-resistant *Staph. aureus* and a *B. proteus* was recovered during the proteolytic phase. This same combination of organisms has been encountered in nine of the wounds of other patients under penicillin therapy, without any evidence of proteolysis. Although there were no other organisms common to all the proteolytic wounds, an *alpha* streptococcus was found in several, and clostridial organisms were found in a few.

The late inflammatory reaction occurred in five of the seven patients in whom a proper follow-up was obtained. (Two of the nine patients were obliged to leave this region soon after discharge from the hospital.) One of the two patients not developing the late inflammation was injected with autogenous staphylococcal vaccine in an effort to prevent it (Case 168, see below under Immunity). None of the nine patients having wounds with the penicillin-resistant staphylococcus and *B. proteus* combination, but without proteolysis, had a late inflammatory reaction. Cultures were not obtained in the stage of the late inflammatory reaction, but it is believed that the staphy-

lococcus is involved (see below under Immunity). Up until the time of healing both organisms had been consistently present.

Because this type of proteolytic wound had never been observed by us before, and because all of the patients were on penicillin therapy, it is a temptation to ascribe this proteolytic process to the penicillin-resistant staphylococcus.* It is possible, of course, that chance prevented its occurrence in the sulfonamide-treated patients, or that it was not observed, when present, in these or in burn patients seen before the days of chemotherapy.

The wounds have proven stubborn in healing. All methods of local therapy, including gramicidin, have been tried, largely without success. Attempts to find another common factor have proved unsuccessful. Cachexia was present in one patient at onset, but the wound did not heal with improved nutrition. All of the patients received a high vitamin (including 1 Gm. of cevitamic acid a day), high caloric, high protein diet, comparable to that given to other patients. No evidence was obtained of any different pattern of the 17-ketosteroid excretion or creatinuria from those patients without comparable wounds.

That the staphylococcus was implicated, by more than mere presence, is suggested by the fact that eventual healing in the most stubborn of the wounds was achieved only after specific immunity with rise in agglutinin titer was obtained by injections of autogenous staphylococcal vaccine (Case 168, see below under Immunity).

Immunity.—The control of invasive staphylococcal infection and the healing of full-thickness burn wounds infected with the staphylococcus, may involve immune reactions or considerations beyond local surface treatment and specific antibacterial chemotherapy in the form of penicillin. The immune reactions presumably are both specific and nonspecific. They have been encountered during the study of patients with wounds showing the proteolysis of the staphylococcus and *B. proteus,* described in the preceding section, and with invasive staphylococcal infection not controlled by large doses of penicillin. The staphylococcus in both its penicillin-sensitive and resistant forms has been involved. The specific immune reaction measured was the blood serum's agglutinating power of the specific staphylococcus infecting the patient. The nonspecific tests included the blood serum globulin, euglobulin, pseudoglobulins I and II, albumin and total protein. The situation in which immune reactions are believed to be involved are illustrated by the following case reports:

CASE REPORTS

Immunity and the Healing of Proteolysis: Case 168 illustrates spectacular repeated wound healing and wound recession of proteolytic type, with concurrent change in the titer of agglutinins to the staphylococcus. Final healing was achieved, coincidentally, with vaccine therapy and maintenance of a high agglutinin titer.

* This same proteolytic process was incidentally seen at the Hartford Hospital, at the invitation of Dr. Donald Wells, in one of the victims of the circus fire, in the 4th week after injury. This patient had also been on penicillin therapy.

A 34-year-old housewife was transferred to this hospital 37 days after receiving extensive deep burns when her house burned down. She had been treated with both sulfonamide and penicillin therapy before coming to this hospital. On entry, she ran a high, spiking fever. Extensive full-thickness wounds of both arms, back, and front of the chest showed signs of deep infection. The patient had been on a "slimming" diet before her injury and had managed to lose 25 pounds. She was thin and cachectic on arrival here, but on a high vitamin, high caloric, high protein diet made a rapid weight gain in the first six-weeks' period. She was given a high dosage of penicillin therapy, with slow subsidence in the febrile reaction.

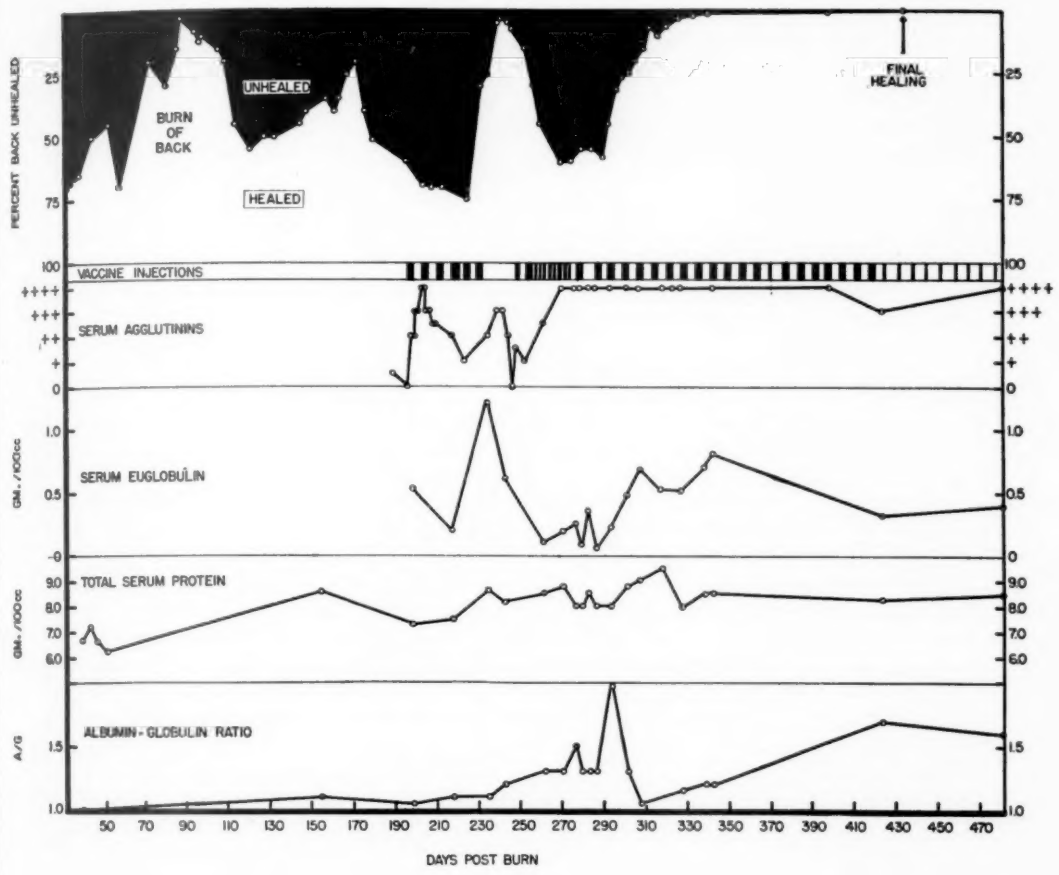


CHART 13

CHART 13.—Case 168: Proteolysis (Wound Dissolution) and Significance of Immunity to Healing: An extensive full-thickness burn wound of the back, 15 per cent of the body surface of a 34-year-old housewife. Thrice nearly healed and thrice dissolved with the fourth and final healing 14 months after injury, coincidentally with a rise in specific immunity. (The patient was transferred to this hospital 36 days after injury; five weeks later, closure of the full-thickness burns of the arms was achieved by grafting.) The back wound was infected with penicillin-resistant *Staph. aureus* and *alpha hemolytic Streptococcus* and *B. proteus*. Penicillin was administered until the 150th day after injury. Autogenous staphylococcus vaccine was started on the 197th day, stopped on the 235th day, resumed on the 250th day, and continued until after healing. The last two waves of healing followed rises of staphylococcal agglutinin titer and coincided with rises of serum euglobulin concentration.

The original burn slough was irregularly distributed over the full-thickness burns on entry. During the first four weeks of her stay in this hospital, concomitant with her nutritional improvement, spontaneous epithelization of the wounds started. Five weeks after admission the wounds of both arms and parts of the back were grafted with mosaic grafts. These took well, and there was rapid closure of the wounds of the arms. Subsequent graftings of the wounds of the back and the front of the chest did well initially, the wounds almost closing. On the 8th week after entry, however, the 95th day after injury, the proteolytic process appeared in the wounds of the back and anterior chest and loss of grafts began (Chart 13). By the 120th day after injury virtually all the wounds of the back and anterior chest had reopened. The wounds of the arms remained healed. Various local measures, including gramicidin, were tried in succession. Systemic penicillin was continued throughout. By the 150th day, wound healing was again apparent but the wave of healing was only temporary. By the 190th day proteolytic dissolution of the wounds was once more gaining. Since the patient had achieved an apparently good nutritional state and since the systemic penicillin and the variety of local measures tried had been without effect in ridding the wounds of the proteolytic process or the penicillin-resistant staphylococcus and *B. proteus,* stubborn bacterial inhabitors of the wounds, a trial of staphylococcal vaccine was considered. The agglutinin titer to the persistent *Staph. aureus* proved to be a trace, or 0. The vaccine was, therefore, started on the 197th day, by intramuscular injection, and within a week there was an apparent response, the agglutinin titer rising abruptly to ++++ (Chart 13). There was no immediate change in the condition of the wound; indeed, the dissolution had progressed and the vaccine was, therefore, continued.

In the 4th week of vaccine therapy, spontaneous closure of the wound had recommenced and proceeded rapidly. The vaccine injections were discontinued on the 235th day, there being in the serum a +++ titer of agglutinins and 1.2 Gm. of euglobulin. On the 245th day, proteolysis was again apparent in the wound, and the serum agglutinin titer had fallen to 0. The serum euglobulin level had also declined.

In spite of renewed injections of the vaccine on the 250th day, the proteolysis continued until the open wounds of the back were nearly as extensive as they had been before initiation of the vaccine therapy. Enlargement of the wound ceased simultaneously with the return of the agglutinin titer to ++++. Healing of the wound did not recommence, however, for another 20 days, occurring at a time when the euglobulin level once more was rising. This healing phase, the fourth to have occurred, was again from spontaneous regeneration of epithelium; it was prompt and complete. The agglutinin titer remained high throughout the healing period, as did the euglobulin level. During the period when the healing rate was at a maximum the serum total protein level reached the peak of 9.5 Gm. per 100 cc.

The patient was discharged on the 343rd day. Because of the previous tendency of her wounds to dissolve and because of the late inflammatory reaction observed previously in the proteolytic wounds of other patients, the vaccine therapy was continued for another five months. When seen for final follow-up on the 546th day, no inflammatory reaction had appeared. The serum agglutinin titer was ++++.

Immunity and Late Inflammation of Proteolysis: Case 210, illustrating subsidence of the late inflammation following the healing of proteolytic wounds coincidentally with a rise in the blood serum of specific agglutinins to the staphylococcus previously recovered from the patient's wounds.

A previously healthy housewife, age 34, received a flame burn of 31 per cent of her body, five-sixths of which was of full-thickness destruction. Although physiologic balance was never stable, a good part of the full-thickness wounds were excised on the 8th day. Small, thin skin grafts were irregularly distributed over the excised areas on the 13th day. The grafts took successfully but before the grafted wounds had closed by spread of epithelium, proteolysis developed in them and in the unexcised sloughing wounds. For two months the grafts retreated. Final closure of the wounds after further grafting was

achieved by the end of the 4th month. The patient was discharged home on the 128th day after injury.

The patient returned on the 295th day after injury complaining of pain and intense itching of her wounds. Those wounds which had previously harbored the proteolytic process, though firmly epithelized, were swollen, deeply indurated, red and tender, typical of the late inflammation. Fortunately, the virulent, penicillin-resistant staphylococcus recovered from the patient's wounds before healing had been preserved in the laboratory and the patient's blood serum on this day showed a plus two specific agglutinin titer to it. The serum was also found to contain:

Total protein	7.9 gm./100 cc.
Euglobulin	0.3 gm./100 cc.
Pseudoglobulin I	1.7 gm./100 cc.
Pseudoglobulin II	0.9 gm./100 cc.
Globulin	3.0 gm./100 cc.
Albumin	5.0 gm./100 cc.

The patient was not given autogenous staphylococcal vaccine because of the presence of some specific agglutinins. Vitamin C, 2 Gm. per day, was added to her diet.

By the 336th day the late inflammation had subsided. The serum agglutinins were found to have increased to ++++. The euglobulin level had more than doubled. The serum protein findings were:

Total protein	7.6 gm./100 cc.
Euglobulin	0.8 gm./100 cc.
Pseudoglobulin I	1.2 gm./100 cc.
Pseudoglobulin II	0.8 gm./100 cc.
Globulin	2.7 gm./100 cc.
Albumin	4.9 gm./100 cc.

The rise in titer of the specific staphylococcal agglutinin and in the level of the euglobulin concomitant with subsidence of the late inflammation suggests that the staphylococcus known previously to have infested the wounds was in part responsible for the inflammation and that specific immunity in the host plays a rôle in the conquering of the organism. Whether the vitamin C aided the host or whether the rise in immunity would not have occurred spontaneously cannot of course be determined from this case.

Immunity and Invasive Infection: Case 218 illustrates the exhaustion of the immune bodies during the phase of advancing cellulitis uncontrolled by penicillin and eventual healing of proteolytic wounds only with return of specific agglutinins. A 54-year-old heavy-set seaman entered the hospital with limited burns of head and face, hands and feet, considered initially to be of incomplete destruction. The wounds were covered; the patient was started on 240,000 units of penicillin intramuscularly per day. Because of advancing cellulitis in the right forearm a blood culture was taken at 48 hours which showed *Clostridia* and *Staph. albus*, coagulase-negative, penicillin-sensitive. Similar organisms were found in the wounds. Because of the continued advance of the cellulitis the penicillin dosage was doubled. The cellulitis was not effectively controlled until the 9th day, after which time it slowly subsided. After three weeks a proteolytic process was noted in the wound of the right hand and what should have been a burn of incomplete destruction turned into one of full-thickness. A similar process was also apparent in the wounds of the feet. Initial grafting tried on these areas was unsuccessful.

The blood serum agglutinins, measured routinely on entry, were +++. On the 2nd and 4th days during the advancing cellulitis they were ++ and +++ but by the 9th day they were 0. The euglobulin titer was also falling during this period. It appeared possible, therefore, that specific antibodies were being exhausted during the period of the advancing infection which was taking place in spite of the large dosage of penicillin. The euglobulin level fell further, reaching 0 during the phase of proteolytic infection.

Because of the proteolysis and absence of detectable antibodies, vaccine therapy was

initiated. The vaccine was injected on three successive days of each week for four weeks before a return and rise in the agglutinins was observed. The reappearance and rise in euglobulins was longer delayed. Wound healing occurred coincidentally with the euglobulin rise, the agglutinins remaining elevated. Although the latent period between onset of vaccine therapy and agglutinin rise was unusually long, bringing up the question of the efficacy of the vaccine, it is to be stressed that healing, as in Case 168, occurred simultaneously with the rise in the euglobulin level and at a time when the agglutinin titer remained high.

Immunity and Invasive Infection: Case 254 was an extensively burned healthy male, age 38, with scattered full-thickness, electric flash-burns who developed, in spite of continued penicillin therapy, an invasive staphylococcus infection in the week following an extensive grafting procedure. Coincidentally with the invasive infection and abscess formation there was a fall in the immune body titer and with its healing there was a rise.

In the first nine days after injury there was a good and immediate immune response to the staphylococci present in the wounds. The agglutinin titer on the 2nd day was 0 but by the 9th had risen to $^{+++}$. The euglobulin in the same period rose from 0.1 to 0.6 Gm. per 100 cc. The same agglutinin titer was present on the 35th day, though there had been a drop in the euglobulin level to 0.3 Gm. per 100 cc. During these first 35 days there had been prompt healing of the second-degree burns and marginal healing of the full-thickness areas. On the 35th day a multiple grafting operation was performed. Five per cent of the body surface was grafted.

On the 40th day phlebothrombosis was recognized in one leg. Since there were burn wounds covering the usual area of the incision for femoral vein ligation, the phlebothrombosis was treated with intravenous heparin. This was injected into a superficial vein just above the ankle in the leg opposite that showing the signs of phlebothrombosis. This injection was followed 24 hours later by a subcutaneous thrombophlebitis along the calf above the site of the injection and accompanied by a rapidly progressive cellulitis. In order to identify the organism responsible for the cellulitis, on the 46th day an area of necrosis in the cellulitis was aspirated. Culture revealed a virulent *Staph. aureus* identical with that to be found in the wounds; both were penicillin-resistant.

The necrosis in the cellulitis increased and formed a small abscess which was treated successfully with two further aspirations rather than open drainage. The grafts healed satisfactorily during the period of cellulitis and abscess.

It is to be stressed that penicillin, 360,000 units per day intramuscularly, had been continued uninterruptedly throughout the course in the hospital. During the period of abscess formation the agglutinin titer had fallen to plus one on the 46th day. Gradual healing of the abscess occurred coincidentally with the rise in agglutinin titer to $^{+++}$ on the 60th day, and $^{++++}$ on the 70th day. During this period of rise of agglutinin titer, the euglobulin level fell to 0.05 on the 60th day.

CONCLUSIONS

The staphylococcus is destructive and invasive in deep burn wounds of the skin. Its presence is to be anticipated in every wound. In the absence of chemotherapy the number of strains apparently increased, while under systemic sulfadiazine the number was held constant. Under systemic penicillin the number of strains slowly decreased.

The prominence which we have observed the staphylococcus to assume in the infection of the burn wound may conceivably be due to the suppression by chemotherapy of the *beta hemolytic Streptococcus*. The virtual elimination of the rampant streptococcal cellulitis may have destroyed a screen hiding the staphylococcal infection; it is also possible that the *beta* streptococcal infection formally restrained the staphylococcus. The presence of staphylococcal cellu-

litis and bacteremia and the recovery of a greater number of strains of the staphylococcus from the wounds of the burned patients in whom chemotherapy was delayed, however, suggests that staphylococcal infection was present in burn wounds before the days of sulfadiazine or penicillin. It merely failed to attract attention.

Under either sulfadiazine or penicillin the virulence of the staphylococci increased rapidly. On the day of injury three-quarters of the staphylococci were avirulent but by the 6th week this proportion was fully virulent. Even with the gradual reduction in total number of strains under penicillin, there were more fully virulent strains of the staphylococcus in the 6th week than on the day of injury.

Resistance to penicillin developed so rapidly in the staphylococcus and proved of such permanent nature that only within the first three weeks of therapy is the maximum effect of penicillin to be counted upon. On the day of injury but 10 per cent of the staphylococcal strains recovered were penicillin-resistant. By the 6th week of therapy, 90 per cent, including all the fully virulent forms, were resistant.

Proteolysis, or liquefaction of the superficial aspect of a burn wound without deep inflammation, has been encountered in nine patients three weeks, or more, after starting penicillin therapy. The wounds have proved stubborn in healing and after eventual epithelial closure have exhibited later a deep inflammation. The only common factor of these wounds has been the combination of a virulent, penicillin-resistant *Staph. aureus* and a *B. proteus*. Because of the coincidence of the healing of these wounds with a rise in the blood serum of agglutinins specific for the infecting staphylococcus and of the euglobulin level in the patients in whom these measurements were made, it is believed that the staphylococcus is the principal offender and that specific immunity to the staphylococcus is the deciding factor in overcoming the infection. The rôle of the *B. proteus* may be merely that of inhibiting the antistaphylococcal activity of the penicillin, a property which *in vitro* it has been demonstrated to possess.

Other examples of the importance of specific staphylococcal immunity to the control of infection by the staphylococcus in patients receiving penicillin have been found. Invasive infection by the staphylococcus, advancing cellulitis and lymphangitis, and bacteremia, has been repeatedly observed in patients with widespread burn wounds infected with virulent staphylococci and in spite of massive doses of penicillin. In the patients in whom the serum levels of agglutinins and euglobulins have been followed, subsidence of the infection has been accompanied by changes in their levels. The failure of penicillin to achieve control of the infection and the need, therefore, for an immune response by the host may of course have been due to an inadequate concentration of penicillin in spite of the huge dosage. The presence in burn wounds of bacteria inhibiting penicillin and the extensiveness of the infected area may have reduced the drug concentration to an ineffectual level.

Additional evidence for the mutation of staphylococci from one form to

another has been found. An initial action of penicillin appears to transform virulent forms to the avirulent. If the organisms survive, drug resistance develops and reversion to the virulent form follows.

REFERENCES

1 Aldrich, R. H.: Treatment of Burns with a Compound of Aniline Dyes. New England J. Med., **217**, 911, 1937.

2 Colebrook, L., *et al.*: Studies of Burns and Scalds (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942–43). Medical Research Council, Special Report Series No. 249, London: His Majesty's Stationery Office, 1944.

3 Lyons, Champ: The Management of the Cocoanut Grove Burns at the Massachusetts General Hospital: Problems of Infection and Chemotherapy. ANNALS OF SURGERY, **117**, 894, 1943.

4 Chapman, G. H., Berens, C., Nilson, E. L., and Curcio, L. G.: The Differentiation of Pathogenic Staphylococci from Nonpathogenic Types. J. Bact., **35**, 311, 1938.

5 Blair, J. E.: The Pathogenic Staphylococci. Bact. Rev., **3**, 97, 1939.

6 Fairbrother, R. W.: Coagulase Production as a Criterion for the Classification of the Staphylococci. J. Path. and Bact., **50**, 83, 1940.

7 Goyle, A. N., and Minchin, R. L. H.: A Note on the Biochemical and Serological Classification of the Staphylococci. Indian J. Med. Res., **27**, 611, 1940.

8 Spink, W. W., and Vivino, J. J.: The Coagulase Test for Staphylococci and its Correlation with the Resistance of the Organisms to the Bactericidal Action of Human Blood. J. Clin. Invest., **21**, 353, 1942.

9 Chapman, G. H.: Determination of the Chromogenic Properties of Staphylococci. J. Bact., **45**, 405, 1943.

10 Lyons, Champ: Antibacterial Immunity to Staphylococcus Pyogenes. Brit. J. Exp. Path., **18**, 411, 1937.

11 Howe, Paul E.: The Use of Sodium Sulfate as the Globulin Precipitant in the Determination of Proteins in Blood. J. Biol. Chem., **49**, 93, 1921. *Idem.:* The Determination of Proteins in Blood. A Micro-Method. *Ibid.:* **49**, 109, 1921.

12 Spink, W. W., Hall, W. H., and Ferris, V.: Clinical Significance of Staphylococci, with Natural or Acquired Resistance to the Sulfonamides and to Penicillin. J. A. M. A., **128**, 555, 1945.

13 Marziani, R.: Phénomènes de Mutation Présentés par des Staphylocoques, Consécutivement à des Passages par L'Organisme du Cobaye. Bull. Acad. de Méd., Paris, **98**, 527, 1927.

14 Dudgeon, L. S., and Goadbey, H. K.: Further Observations on the Staphylococci, with Special Reference to their Haemolysins and Variability. J. Hyg., **30**, 180, 1930.

15 Pinner, M., and Voldrich, M.: Derivation of Staphylococcus albus, Citreus, and Roseus from Staphylococcus aureus. J. Inf. Dis., **50**, 185, 1932.

(*Continue with Part IV*)

PART IV

THE INCIDENCE, VIRULENCE AND RESISTANCE TO PENICILLIN OF THE STREPTOCOCCUS IN BURN WOUNDS OF PATIENTS TREATED WITH PENICILLIN OR SULFONAMIDES

IN SPITE of the attention bestowed upon the streptococcus as the most reprehensible contaminating organism of the burn wound, there has been a disparity in the reports of its incidence and disagreement regarding its relation to toxemia in the burned patient. Firor and Aldrich[1] were the first to test the concept that the toxemia of burns is a toxemia of wound infection. From a bacteriologic survey of the flora of burn wounds they reported that although but few contaminants, such as the staphylococcus and *B. coli,* were recovered immediately after injury, by 12 hours after injury the wounds of all the severely burned patients and the large majority of the mildly burned, harbored streptococci. Either the *beta* hemolytic or the *gamma* streptococcus was found. They believed that the subsequent toxemia of the patients was explained by streptococcal sepsis. Such a high streptococcal infestation has not been subsequently reported. Neither the number of patients examined nor the relative frequency of the two types of streptococci were recorded, and it is not known, therefore, whether a representative sample of burned patients was studied.

Cruikshank,[2] in 1935, also, recorded a high incidence of streptococci in burn wounds. Of 100 burns examined on admission, 11 were found to harbor hemolytic streptococci. Of 32 burns examined between the 3rd and 6th days, 21, or 66 per cent, revealed the hemolytic type of streptococcus. Ten of 490 burned patients developed scarlet fever. Cruikshank made the significant observation that the same kind of streptococcus was to be found in abundance in the air and dust of the wards housing burn patients, but not in those of other wards. He mentioned the presence of the *alpha* type, *Streptococcus viridans,* in some cultures, but he did not record its incidence in detail.

In spite of Cruikshank's collaboratory evidence, Wilson, MacGregor and Stewart,[3] in 1938, were loath to accept Firor and Aldrich's concept of early streptococcal toxemia. They found infection in superficial burns to be rare in spite of the presence of hemolytic streptococci and although signs of infection and hemolytic streptococci were found in deep burns they concluded that infection was unusual before the 5th day after injury and, as a rule, not obvious until after the 7th day. They, too, gave no details regarding their bacteriologic studies, mentioning only the hemolytic streptococcus as the usual cause of sepsis.

Seven years later than Cruikshank, and in the same Glasgow wards, Colebrook, and his collaborators,[4] found a rise in the incidence of the hemolytic streptococcus in the early hours after injury comparable to that reported by Cruikshank, but the actual incidence throughout was slightly lower. This organism was recovered from 4 per cent of 370 burns in the 1st 12 hours, from 23 per cent of 39 in the 2nd 12-hour period, and 42 per cent of 107 burns cultured after 24 hours. Colebrook records strong evidence for contamination subsequent to hospital admission as the source for the increasing number of hemolytic streptococci. Eleven Griffith-types were found among 37 strains recovered from patients cultured on admission, with no one type predominating.

Subsequently, one Griffith-type clearly predominated, nearly all new cases acquiring a strain of this type. Dust and blankets were incriminated as the carriers. Only passing mention is made of a streptococcus other than the hemolytic; two strains of the *gamma* streptococcus were reported as encountered.

In the Contaminated Wound Project of Meleney,[5, 6] of 1942–43, interest in the streptococcus was also centered in the *beta* hemolytic. No accounting was made of either the *alpha* or *gamma*. It remained for Lyons,[7] to record the first comprehensive account of the distribution of the *beta* hemolytic, *alpha* and *gamma* streptococci in burns. The flora of the full-thickness wounds of nine victims of the Cocoanut Grove fire were studied in detail subsequent to the 1st five days after injury. Streptococci of all three forms were found, and the *alpha* in the greatest profusion. Sixty per cent of the cultures taken at the end of the 1st week contained an *alpha* strain. *Beta* hemolytic strains were recovered from 30 per cent, or less, of the wounds. *Gamma* strains were found least often. The relatively low incidence of the *beta* strains was ascribable to the sulfadiazine which was being systemically administered to the patients, but the high incidence of the *alpha* type was without precedent and unexplained.

Such were the reports of the incidence of the *beta* hemolytic streptococcus in burn wounds at the time this study was undertaken. With each report, from 1933 to 1943, a lesser incidence of this streptococcus was recorded. In judging the effect of penicillin on the *beta* hemolytic streptococcus in burn wounds, an explanation for this decrease in incidence should be sought. Could it have been due to improvement in measures employed to prevent contamination; to a difference in numbers of this streptococcus in the various cities where the studies were made; or to a difference in season when made or to the recent introduction of the sulfonamides? The sulfonamides had been used both locally and systemically in the therapy of the burned patients reported by Meleney and Lyons.

Such were the meager reports of the occurrence of the *alpha* and *gamma* streptococci in burn wounds. Was Lyons' finding of a prominence of the *alpha* type a chance occurrence peculiar to the night club fire or the result of the sulfadiazine therapy? Are the *alpha* and *gamma* streptococci of burn wounds of any clinical significance?

OBSERVATIONS

The streptococci recovered from the burn wounds were subdivided into the *alpha, beta* and *gamma* types. (The *alpha* is the *Streptococcus viridans*, the *beta* is the hemolytic and the *gamma* the nonhemolytic streptococcus). The wounds were of both partial- and full-thickness destruction and of patients treated with either sulfonamides or penicillin. The streptococci recovered from the wounds of patients being treated with penicillin were tested for resistance to penicillin. The coagulase test was also applied to a number of the strains of the *alpha* type recovered from the wounds of the penicillin-treated patients. Search was made for evidence of mutation from one type to another.

Incidence of Types on Day of Injury.—The number and proportion of strains of streptococci per culture recovered on the day of injury differed in the groups of patients treated with either sulfadiazine or penicillin. The major-

ity of the patients treated with sulfadiazine were studied in the two years previous to the introduction of penicillin, and the initial cultures of the wounds of these patients were made from débrided tissue. Seven strains of streptococci were recovered from the 13 cultures of the full-thickness wounds (Chart 14), and 16 strains from the 29 cultures of the partial-thickness wounds (Chart 17), an incidence in each of 55 per cent. The *beta* hemolytic type accounted for three of the strains from the full-thickness, and but one from the partial-thickness wounds. The remaining strains were of the *alpha* type.

The patients treated with penicillin were studied from January, 1944 through December, 1945. The cultures from the wounds of these patients were by the swab technic on the day of injury, as well as later; a larger number of wounds was cultured and a lower incidence of streptococci was found. Streptococci were recovered from 30 per cent of the wounds. No *beta,* 19 *alpha,* and two *gamma* strains were recovered from the wounds of full-thickness, 69 wounds having been cultured (Chart 15). One *beta,* nine *alpha,* and no *gamma* strains were recovered from the 31 wounds of partial-thickness (Chart 18).

Incidence of Types after Day of Injury and without Chemotherapy.—The chance to observe possible changes in the incidence of the streptococci occurring in the absence of chemotherapy, was obtained in the wounds of the 19 patients whose admission to the hospital was delayed and who had received no chemotherapy, local or systemic, prior to entry. Admission of the patients varied from 1 to 30 days after injury, an average of 7.2 days. From the 45 cultures taken on entry and before chemotherapy, 40 strains of streptococci were recovered (Chart 16). Twenty-eight of the strains, or 70 per cent, were of the *alpha* type. Only eight of the strains were of the *beta* and four of the *gamma* type. These patients were studied throughout the same period as the groups receiving penicillin from the day of injury. Some had been treated at home, some in other hospitals prior to entry to this hospital.

Incidence of Types during Sulfadiazine.—In the 1st week after injury in the full-thickness wounds of the patients who were being treated systemically with sulfadiazine, there was an abrupt rise in incidence of the streptococci to a level 60 per cent higher than on the day of injury (Chart 14). During the 2nd and 3rd weeks there was an equally precipitous decline in the incidence to a level approximately half that of the day of injury. Both the rise and fall were due almost entirely to changes in the number of *alpha* strains. After the 3rd week the number of the *alpha* strains remained approximately constant until their final disappearance on the 56th day. The number of *beta* strains remained nearly constant from injury until the 6th week, when there was a decline, with disappearance on the 48th day. On this day, also, all the *gamma* streptococci had disappeared; at any one time but few *gamma* streptococci were recovered.

In the wounds of partial-thickness of the patients who were receiving sulfadiazine there was no increase in incidence of the *alpha* type; there was instead a decline in the 1st two weeks followed by a rise in the 3rd (Chart 17). The *beta* hemolytic type increased slightly in incidence in the 1st two weeks. There was a slow rise in the number of the *gamma* type in the three weeks during which the wounds remained open.

Incidence of Types during Penicillin.—There was a three-fold rise in the

incidence of the streptococci in the full-thickness wounds during the first week of penicillin therapy (Chart 15). The levels reached in the 1st week were maintained in the 2nd. Although there was a decline following this initial rise, it did not occur until the 3rd week, and in contrast to the findings in the sulfadiazine treated patients, it constituted only a partial return to the initial incidence. At the lowest level of this decline, at the end of the 3rd week, the number of strains was still twice as many as on the day of injury. Again in contrast to the sulfonamide cases from the 4th week on the number was again increasing. By the 55th day the number had surpassed the peak of the 1st and 2nd weeks.

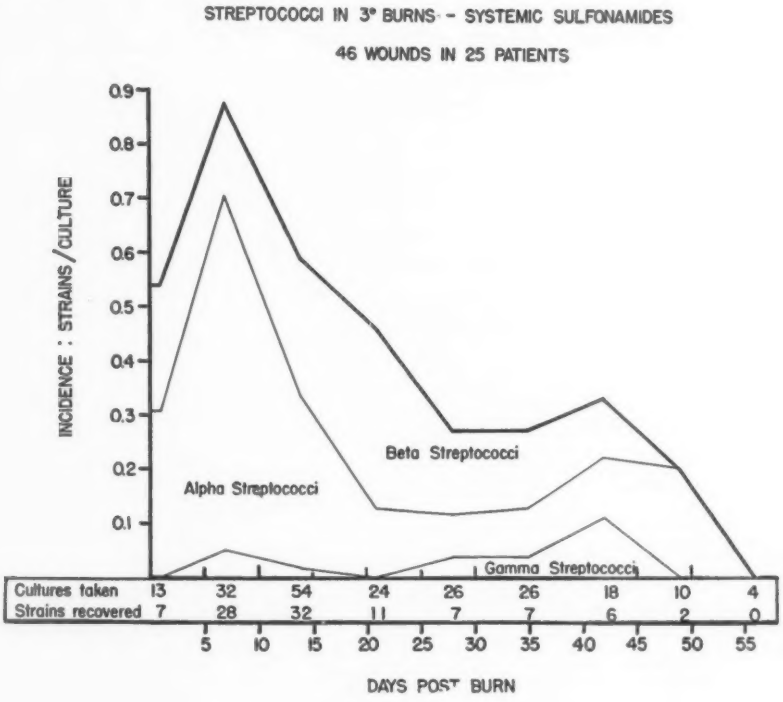


CHART 14

CHART 14.—The Incidence of Streptococci in the Flora of Full-thickness Burn Wounds in Patients Receiving Sulfonamide Therapy: The streptococci isolated from 46 wounds of 25 patients (same patients as in Charts 3 and 8 of Parts I and III) are classified according to the type of hemolysis produced on the blood-agar medium.

A few *beta* strains were recovered in the 1st week. During the succeeding three weeks there was little change in their number and by the end of the 5th week they had virtually disappeared. The number of *beta* strains encountered throughout the period of treatment in these patients was significantly less than in the sulfonamide-treated cases. Although the number of *gamma* strains increased in the 1st week, their number was never large and any fluctuation was not notable. The changes in incidence of the *alpha* type accounted for most of the changes in the over-all incidence of the streptococci. With but 30 per cent of the wounds containing an *alpha* or a *gamma* streptococcus on the day

of injury, by the 57th day 90 per cent of the wounds had an *alpha* streptococcus and a majority of the remaining wounds harbored a *gamma* strain, and a few wounds both. This incidence of the three types of streptococci is again in contrast to the wounds of the sulfonamide-treated cases, which by this time had lost all streptococci.

The changes in incidence of the three types of streptococci following the onset of penicillin therapy in the full-thickness wounds of the patients whose hospital admission and chemotherapy were delayed (Chart 16), were comparable to those encountered following the 2nd week of therapy in the patients

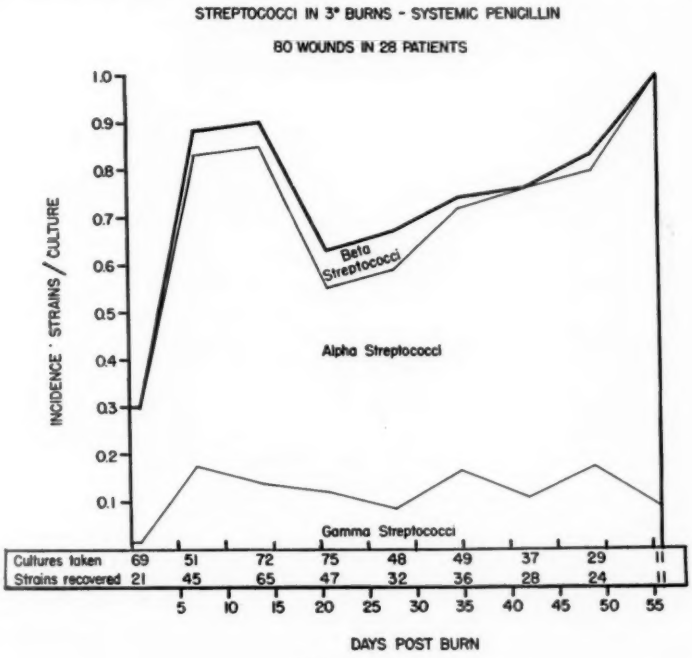


CHART 15

CHART 15.—The Incidence of Streptococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: The streptococci isolated from 80 wounds of 28 patients (same patients as in Charts 1, 6, 9 and 10 of Parts I, II and III) are classified according to the type of hemolysis produced.

whose penicillin was started on the day of injury. At entry, there were three times as many streptococci as on the day of injury in the other group of penicillin-treated patients and more than were ever found in the sulfonamide-treated patients. The *beta* strains had virtually disappeared at the end of the 3rd week of therapy. There was an initial decline in the number of the *alpha* strains followed by a continuous rise. In the 6th and 7th weeks of therapy the number of *alpha* streptococci exceeded that at entry. The number of the *gamma* type fluctuated somewhat more than in the previous group.

In the partial-thickness wounds of the patients treated with penicillin the single *beta* strain disappeared in the 1st week, the *alpha* strains remained constant in the 1st two weeks, declining slightly in the 3rd, and the one strain of the *gamma* type encountered was found at the end of the 1st week (Chart 18).

Penicillin Resistance.—The resistance to penicillin of all the streptococci recovered from the wounds of patients being treated systemically with penicillin was measured *in vitro.* No change in the penicillin resistance of the *beta* hemolytic streptococci was found to occur during the course of the penicillin therapy. This finding is in conformity with the earlier report of Rammelkamp and Maxon.[8] Considerable variation in the resistance of the various strains recovered, however, was observed; some were very sensitive, others

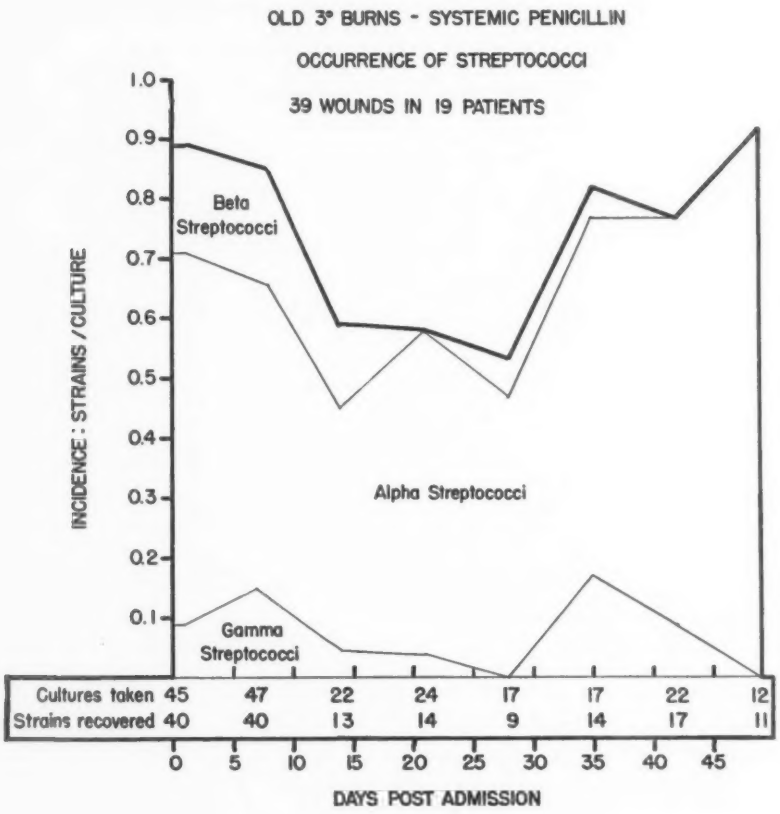


CHART 16

CHART 16.—The Incidence of Streptococci in the Flora of Full-thickness Burn Wounds of Patients Whose Hospitalization and Penicillin Therapy were Delayed: The streptococci isolated from 39 wounds of 19 patients (same patients as in Charts 2 and 7 of Parts I and II) are classified according to the type of hemolysis produced.

resistant. Because of the lack of change in resistance during therapy, the *beta* hemolytic streptococci are omitted from the charts in which the over-all change in resistance is depicted (Charts 19 and 20).

Both the *alpha* and *gamma* streptococci rapidly developed a resistance to penicillin. The resistance was proportionate in the two types to their incidence. In the wounds of the patients whose penicillin therapy started on the day

of injury, only 25 per cent of either organism were resistant on the day of injury, whereas by the 50th day 83 per cent were resistant (Chart 19). In the wounds of the patients whose penicillin therapy was delayed, slightly more, 30 per cent of the *alpha* and *gamma* streptococci, were resistant before onset of therapy (Chart 20). In the 4th week more than 80 per cent were resistant. In this group of patients, the number of sensitive strains increased after the 4th week, but during the same period that of the resistant strains was also increasing. By the 48th day, approximately two-thirds of the *alpha* and *gamma* types were resistant.

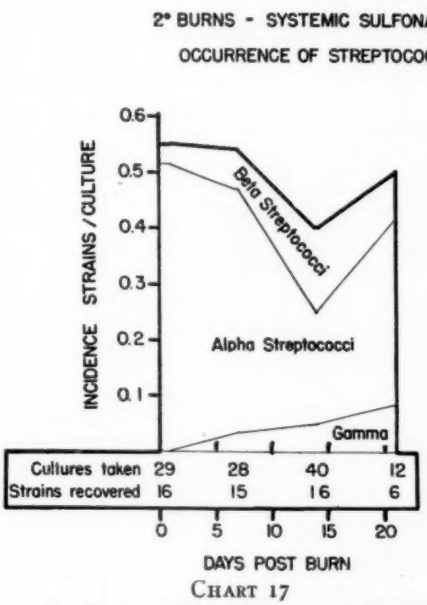


CHART 17

CHART 17.—The Incidence of Streptococci in the Flora of Partial-thickness Burn Wounds of Patients Receiving Sulfonamide Therapy: The streptococci isolated from 58 wounds of 35 patients (same patients as in Chart 4 of Part I) are classified according to the type of hemolysis produced.

Streptococcal Survival beneath the Closed Wound.—Four cases were encountered which indicated that the *beta* hemolytic streptococcus is able to survive the chemotherapy and superficial wound healing. After at least four weeks of continuous sulfonamide or penicillin therapy and complete epithelial closure of the burn wounds, four patients returned to the hospital one to four weeks after discharge with recurrent streptococcal infection deep in the wounds. One patient, who had had a partial-thickness burn, had been given sulfonamide therapy; the other three had had full-thickness burn wounds and had received prolonged penicillin therapy. On readmission, in each case the same strain of *beta* hemolytic streptococcus which had been found in the wounds before healing was recovered by needling the wound. There was prompt subsidence of the invasive inflammation after renewal of the chemotherapy. The cultures taken during the two-week period before healing in the sulfadiazine-treated and two of the penicillin-treated patients had not shown the streptococcus.

Virulence.—The coagulase test, similar to that used on the staphylococci, was applied to a number of the *alpha* streptococci recovered from the wounds of the penicillin-treated patients. A trend of increasing coagulase activity with the development of penicillin resistance was noted. No consistent change in the inflammation of the wound or in the clinical condition of the patient was observed which correlated with this change in coagulase activity. It was, therefore, not ascertained whether this test is an indication of virulence of

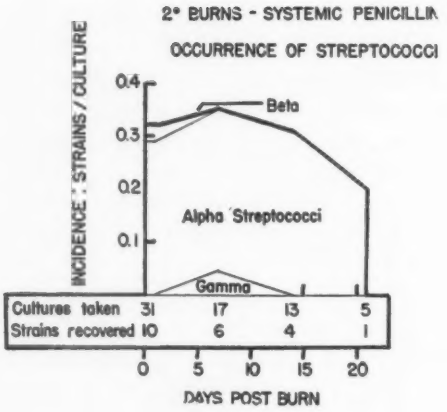


CHART 18

CHART 18.—The Incidence of Streptococci in the Flora of Partial-thickness Burn Wounds of Patients Receiving Penicillin Therapy: The streptococci isolated from 35 wounds of 18 patients (same patients as in Chart 5 of Part I) are classified according to the type of hemolysis produced.

the streptococcus as it is of the staphylococcus.

Mutation. — The rapid disappearance of the *beta* hemolytic streptococcus during penicillin therapy and the simultaneous increase in incidence of the *alpha* and *gamma* forms poses the question of a streptococcal mutation from *beta* to *alpha* or *gamma*, and *gamma* to *alpha*. No consistent sequence of change from one type to another has been noted in wounds from which but one streptococcal strain has been recovered, comparable to that encountered when but one staphylococcal strain was recovered. Evidence for a mutation of the streptococcus *in vivo* in burn wounds is, therefore, lacking.

CONCLUSIONS

It was expected, from the writings of Aldrich, Cruikshank, Colebrook and Meleney, that streptococci would abound in burn wounds but it was not expected that so few of the *beta* hemolytic type, so many of the *alpha* on the day of the injury, and such a profusion of the *alpha* and *gamma* types during the course of penicillin therapy would be found. The incidence of the *beta* hemolytic streptococcus in wounds both on the day of injury and of those of patients whose admission was delayed, was lower than had previously been reported. Could this be ascribed to an attention to prevention of contamination?

Colebrook has emphasized that the *beta* hemolytic streptococcus is not an usual inhabitant of the skin but that the dust of the hospital and ambulance and hospital blanket are likely to be heavily populated with this organism. He deduced that it is from such extraneous sources that burn wounds become contaminated with this type of streptococcus. Inspired by Colebrook, measures to prevent contamination were introduced during the course of this study. Formerly, and during the sulfonamide era, the community was not so burn conscious and not so scrupulous in the emergency handling of burn patients. After the Cocoanut Grove disaster, and at the time when penicillin became available, the physicians of several industries and the staffs of neighboring hospitals were collaborating and forwarding to this hospital their most severely burned patients. Their hospital and ambulance attendants were instructed to use sterile cotton sheets rather than blankets. On arrival at this hospital the patients were promptly placed in an operating room where

examination and initial care were carried out with precise aseptic technic.

The low incidence of the streptococcus found on the day of injury can probably be ascribed to a new emphasis on prevention of contamination. It is not to be ascribed to a seasonal variation since this study was continuous for two years. The low incidence of the *beta* hemolytic streptococcus found in these same wounds subsequently, during the penicillin therapy, as compared

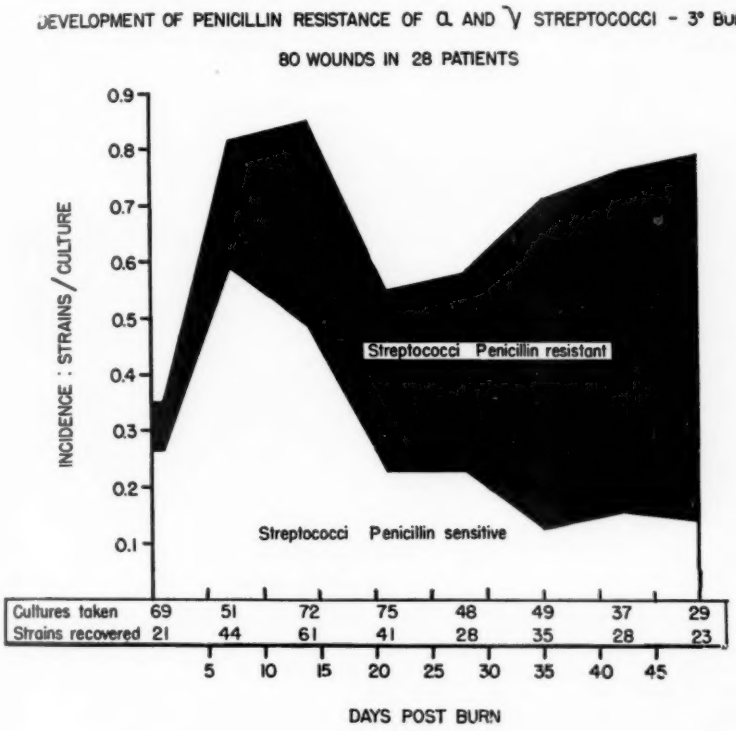


CHART 19

CHART 19.—The Penicillin Resistance of the *Alpha* and *Gamma* Streptococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: The *alpha* and *gamma* streptococci isolated from 80 wounds of 28 patients (cf. Chart 15) were tested for resistance to penicillin. Since the penicillin sensitivity of the *beta* hemolytic streptococcus remained *in vitro* unaltered during the course of penicillin therapy, the strains of this type are omitted from the chart.

with those of the patients treated with sulfadiazine, may be due as much to this emphasis on the prevention of contamination as to the penicillin. Only a few of the patients treated with sulfadiazine were cared for late in the study after penicillin had become available and at a time when the prevention of contamination was being stressed.

More *alpha* streptococci were found in the burn wounds of patients on entry and before chemotherapy was started than had been anticipated and only because the incidence of the *alpha* streptococcus (as well as of the *gamma*) had not been hitherto reported.

The profusion of both the *alpha* and *gamma* types during penicillin therapy was unexpected, particularly since their incidences were so out of proportion to that of the *beta* hemolytic type.

The reason for the profusion and disproportion of incidence of the three types of streptococci during penicillin therapy, however, is explainable when

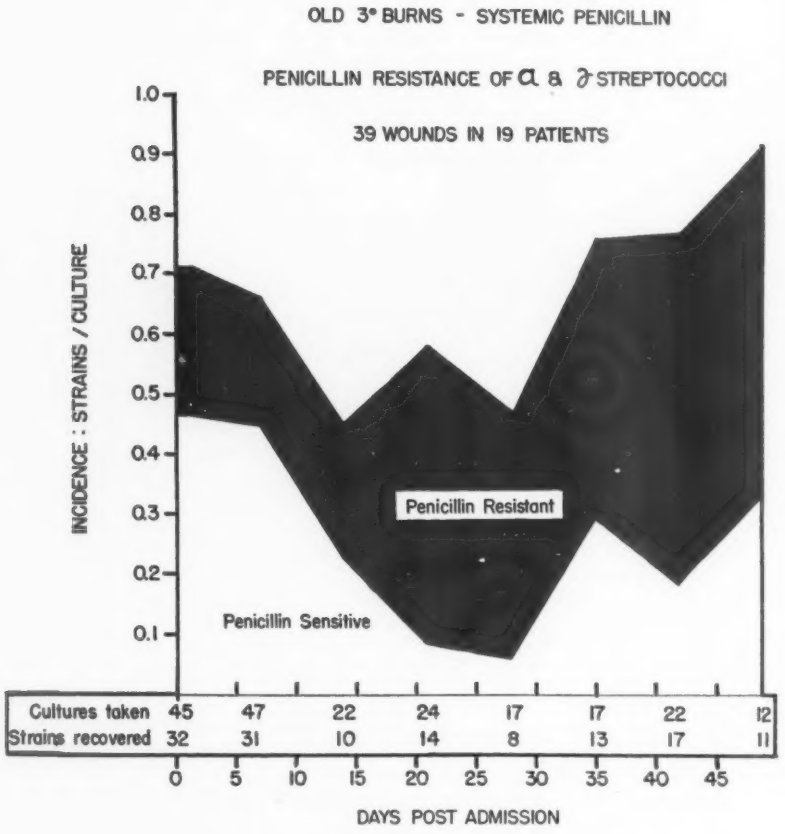


CHART 20

CHART 20.—The Penicillin Resistance of the *Alpha* and *Gamma* Streptococci in the Flora of Full-thickness Burn Wounds of Patients Whose Hospitalization and Penicillin Therapy were Delayed: The *alpha* and *gamma* streptococci isolated from 39 wounds of 19 patients (cf. Chart 16) were tested for sensitivity to penicillin. The *beta* hemolytic streptococci are omitted as from Chart 19.

the *in vitro* studies of the resistance to penicillin are taken into account. The *beta* hemolytic type is unable to alter its metabolism to resist penicillin; it is eliminated.* The *alpha* and *gamma* types, on the other hand, rapidly develop a resistance, survive, multiply and spread.

* It is possible that the slightly greater incidence of the *beta* hemolytic streptococcus in the sulfonamide-treated cases found during the course of therapy was due to its development of resistance to sulfadiazine rather than to the early lapses in preventing contamination. Such drug-fastness has been reported by Colebrook.[4]

Since the *alpha* and *gamma* streptococci were controlled better by sulfadiazine and the *beta* by penicillin, it is conceivable that penicillin and sulfadiazine should be combined in the therapy of patients with deep burns. Only a few of our patients were treated systemically with both of these drugs simultaneously, and too few observations were made for any proof of benefit from such combined therapy. The value of combined therapy depends upon how pernicious the *alpha* and *gamma* organisms are judged to be. The rôle of the *beta* hemolytic streptococcus is unquestioned; its presence in burn wounds is clinically associated with invasive infection, fever and delirium.

The rôle of the *alpha* and *gamma* streptococci in burn wounds is a matter of speculation. Both types are undoubtedly the cause of disease in other body regions. The *alpha* streptococcus recovered from these burn wounds is the same type as that associated with subacute bacterial endocarditis; certain other surgical infections;[9] and, occasionally, pneumonia in children and young adults.[10] The *gamma* streptococcus is sometimes the micro-aerophilic organism encountered in the undermining ulcer of Meleney and in nonbacillary gangrene. It is also an enterococcus found in the intestinal tract and surmised to be a salient pathogen of mixed infections of the peritoneal cavity. In the burn wound, the *alpha* streptococcus, penicillin-resistant, was commonly, but not always, present in those wounds showing proteolysis. Although no characteristic type of wound inflammation was typical of the presence of either the *alpha* or *gamma* streptococcus, it certainly cannot be concluded, in view of their pathogenicity elsewhere, that they can be dismissed as of no importance in a burn wound. The patients with these organisms in their wounds were sufficiently ill to be hospitalized.

Because of the postulated perniciousness of the *alpha* and *gamma* streptococci in the burn wound it is advised to combine sulfadiazine with penicillin in the therapy of the extensively and deeply burned patient. Since the sulfadiazine is toxic, particularly to the kidney of the dehydrated patient, it is wise to withhold it until an adequate fluid balance is assured.

COMMENT

Infection of the deep burn wound still exists—this study has not eliminated it. It is of mixed bacterial origin, dependent upon the presence of dead tissue, and inadequately controlled by the known chemotherapeutic agents. Its nature is such, and its toxins so mysterious, that there is still a goodly amount of "trial-and-error" involved in the healing of an extensively and deeply burned patient.

Measures designed to avoid bacterial contamination are tried so that there will be fewer bacteria to flourish in the wound.

Measures are chosen in the attempt to starve, remove or kill those bacteria which circumvent the efforts to reduce contamination. The quickest way to starve the bacteria is to remove their favorite food—the slough—by surgical excision. The way to remove the greatest number of bacteria is, also, by excision of the slough, where they have taken refuge.

To kill the bacteria in the wounds which are not excised and not grafted immediately following excision, a combination of penicillin, sulfadiazine and

streptomycin is to be tried. The penicillin, in massive doses, will be the most effective in reducing the number of *beta* hemolytic streptococci and in preventing invasion by the staphylococcus. Its use will be followed by resistant forms of the staphylococcus and of the *alpha* and *gamma* streptococci. The sulfadiazine should be tried in the hope that it will check the profuse growth of the *alpha* and *gamma* streptococci which have become penicillin-resistant. The streptomycin should be tried, also, in the hope that it will abolish the gram-negative bacilli which penicillin allows to flourish and which inhibit the action of the penicillin.

Neutralization of tetanus and clostridial toxins by administration of their respective antitoxins is indicated, particularly in patients with wounds of the buttocks, thighs and legs. (Diphtheria and scarlet fever antitoxins will rarely be needed.)

The patient is not passive as he watches us try to heal his wounds. He, too, can kill bacteria and neutralize their toxins. He will collaborate the better if we help him regain and maintain his physiologic balance.

The problem of the infection of burns will not be solved in the future by repeating a bacteriologic study with the introduction of a new chemotherapeutic agent. This study informs us of the character of the enemy. In the combat, chemotherapy will be a weapon but the replacement of trial-and-error will come only with a better understanding of the toxins of the bacteria and the immune processes of the host.

SUMMARY

A bacteriologic study of the floras of burn wounds has been made, and the effectiveness of penicillin in controlling infection has been judged. The floras of 80 full-thickness wounds of 28 patients treated with penicillin during 1944-45 have been compared with those of 46 similar wounds of 25 patients treated with sulfadiazine during 1942–43. Likewise, and during the respective periods for each drug, the floras of 35 partial-thickness wounds of 18 patients treated with penicillin were compared with those of 58 wounds of 35 patients treated with sulfadiazine. The floras of 39 full-thickness wounds of 19 patients whose admission to the hospital and onset of chemotherapy were delayed and who were subsequently treated with penicillin, were compared with the 80 wounds of the 28 patients whose penicillin therapy was started on the day of injury.

Neither sulfadiazine nor penicillin exerts more than a limited control over the growth of bacteria in the deep burn wound. The staphylococcus was found to be a contaminant of every wound, and the number of its strains to multiply in the absence of chemotherapy. The multiplication did not occur with sulfadiazine therapy and the number of strains recovered slowly decreased during penicillin therapy. Resistance to penicillin developed rapidly, however, and avirulent gave place to virulent forms. The staphylococcus was judged to be a destructive organism in burn wounds. Evidence for the need of immunity to it was obtained.

No *beta* hemolytic streptococci were recovered on the day of injury from

the full-thickness wounds of the patients subsequently treated with penicillin, and very few from the partial-thickness wounds, in contrast to those whose admission was delayed and to the sulfadiazine-treated patients of the previous two years. It is surmised that improved precautions against wound contamination were the cause of this low incidence. There was more prompt elimination of the *beta* hemolytic streptococcus by penicillin than by sulfadiazine from those wounds in which this organism was encountered. This is presumably related to the observed inability of this streptococcus to develop resistance to penicillin.

The *alpha* and *gamma* streptococci slowly disappeared from the wounds of patients treated with sulfadiazine. In the wounds of the penicillin-treated patients, in contrast, these streptococci grew and spread in profusion until by the 8th week, 90 per cent of all the unhealed wounds contained an *alpha* strain and a majority of the remainder, a *gamma* strain, and a few both. These two streptococci were found to develop rapidly a resistance to penicillin.

The number of strains of the gram-negative bacilli increases rapidly in the 2nd week of penicillin therapy. The consistency of this increase with penicillin and its absence in patients receiving sulfadiazine or no chemotherapy, suggests that it is in some manner induced by the penicillin. These organisms were found *in vitro* to inhibit the action of penicillin.

Wounds of the buttocks, thighs and legs showed the greatest contamination with the highest incidence of the *Clostridia* and the *gamma* or fecal type of streptococcus. Wounds of the head and neck revealed the least contamination with no *gamma* streptococci and but few *Clostridia*. The amount of contamination of the wounds of the upper extremities lay midway between the other two body areas. It is suggested that clostridial antitoxin be considered in addition to tetanus antitoxin and prompt excision of slough in the therapy of patients with full-thickness wounds of the lower extremity.

The rapid development of resistance to penicillin by the previously sensitive staphylococci and streptococci and the profusion of penicillin inhibiting and insensitive gram-negative bacilli indicate that the effective period of penicillin therapy is sharply limited to the 1st three weeks. By six weeks after injury the wounds have become a bacterial quagmire.

The infection of burns is a problem of deep burns. The fight against it combines prevention of contamination, starvation of the bacteria by prompt excision of slough, an attack by penicillin, streptomycin and sulfadiazine, and bolstering the immune processes of the host by restoration and maintenance of physiologic balance of the patient.

REFERENCES

[1] Aldrich, R. H.: The Rôle of Infection in Burns: The Theory and Treatment with Special Reference to Gentian Violet. New Eng. J. Med., **208**, 299, 1933.

[2] Cruickshank, R.: The Bacterial Infection of Burns. J. Path. & Bact., **41**, 367, 1935.

[3] Wilson, W. C., MacGregor, A. R., and Stewart, C. P.: The Clinical Course and Pathology of Burns and Scalds under Modern Methods of Treatment. Brit. J. Surg., **25**, 826, 1937–38.

[4] Colebrook, L., *et al.*: Studies of Burns and Scalds (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942–43). Medical Research Council, Special Report Series No. 249, London: His Majesty's Stationery Office, 1944.

[5] Meleney, F. L.: The Study of the Prevention of Infection in Contaminated Accidental Wounds, Compound Fractures and Burns. ANNALS OF SURGERY, **118**, 171, 1943.

[6] Meleney, F. L.: A Statistical Analysis of a Study of the Prevention of Infection in Soft-part Wounds, Compound Fractures, and Burns, with Special Reference to the Sulfonamides. Surg. Gynec. Obst., **80**, 263, 1945.

[7] Lyons, Champ: The Management of the Cocoanut Grove Burns at the Massachusetts General Hospital: Problems of Infection and Chemotherapy. ANNALS OF SURGERY, **117**, 894, 1943.

[8] Rammelkamp, C. H., and Maxon, T.: Resistance of Staphylococcus aureus to the Action of Penicillin. Proc. Soc. Exp. Biol. & Med., **51**, 386, 1942.

[9] Naffziger, H. C., Warmer, H., Stern, W. E., Fenlon, R., and McCorkle, H. J.: Penicillin in Infections Involving the Central Nervous System and Skull. J. A. M. A., **131**, 1183, 1946.

[10] Thomas, L., Mirick, G. S., Curnen, E. C., Ziegler, J. E., Jr., and Horsfall, F. L., Jr.: Studies on Primary Atypical Pneumonia. II. Observations Concerning the Relationship of a Non-Hemolytic Streptococcus to the Disease. J. Clin. Invest., **24**, 227, 1945.

BRIEF COMMUNICATIONS

EXPERIENCES WITH SYMPATHECTOMY FOR SEQUELAE OF TRENCH FEET

MAJOR A. KRONTIRIS*

ATHENS, GREECE

IN THE ANNALS OF SURGERY, of July, 1945, we read the article by Lt. Col. James Kirtley, Jr., entitled "Experiences with Sympathectomy on Peripheral Lesions." Among the various lesions upon which he applied sympathectomy as a method of treatment, the writer mentions the results he obtained for sequelae of "trench feet."

During the last war, in which Greece had been obliged to engage herself, in the year 1941, against the Italians in Albania in full midwinter, the Greek Army, composed of about 400,000 combatants, was struck, in the form of an epidemic, by "trench feet"; the cases having amounted to 25,000 in number. It is easy to understand that during the following years, when Greece was under German occupation, *i.e.*, 1942-1943-1944, we were compelled to cure a large proportion of these patients for sequelae of "trench feet."

Among the various methods of treatment, we, in some cases, applied sypmathectomy, and communicated our results to the Medico-Surgical Society of Athens. As they only partially coincide with the results published by the above mentioned author, and possess the added advantage of having been under observation during a longer period (more than two years), we wish to publish them so that, whoever is interested in that question, might form a more complete opinion on it. Our cases, 27 in number, dealt with patients who showed sequelae of "trench feet," dated from a long period, and exhibited the following physical signs:

(1) Cyanosis, especially when the feet were dependent.
(2) Gangrene of toes or ulceration of the skin.
(3) Trophic changes of the skin.
(4) Excessive sweating from pearly white, papular lesions on skin, with or without ulceration.
(5) Neuralgic pains.

Before the operation, the peripheral pulsations were taken with the Pachon manometer. They were always found considerably diminished, either by comparison to the other limb, if it was in a healthy condition, or by comparison to the upper extremities, or to the general pulsations of the lower extremities, in cases where both had been attacked.

We have, also, not omitted to study the temporary beneficial effect in most cases of the injection of novocaine into the sympathetic block.

* Lecturer of Athens University, Director of Surgical Department, 421st Military Hospital, Athens, Greece.

We have employed that very method as one of the preoperative indications of the action of the operation. The results obtained by sympathectomy can be divided into two categories: (1) Immediate results; and (2) delayed results.

Immediate Results.—It has been observed that, a few hours after the operation, the local temperature rises considerably. The pains, strong or slight, as also the numbness from which the patient had been suffering, were lessened and proceeded towards total recovery day-by-day.

In cases of hyperhydrosis which, as known, is one of the most serious complaints of the patients, we have noticed that it disappears on the following day, never to return.

Delayed Results.—These concern chiefly cases of ulcerations. Sympathectomy does not seem to have a great effect upon ulcerations. In summary, the following could be said on that subject:

(1) That as long as the ulcerations are situated in the lowest part of the leg, they are healed rapidly and permanently.
(2) If they concern stumps of the feet, not according to type, in the articulation of Lisfranck and Schopart, or if they are placed on the heel, their cure is long and difficult. In the case of a complete cure, the epidermic covering was so thin, that it cracked with the first attempts of the patient to walk.

We do not omit to remark that we have more than once obtained, at a second trial, a good epidermic result with a plastic operation, either through the method of Thiersch, or through the Italian method.

Considering the general rule, according to which plastic operations upon "trench feet" are not always a success, we must attribute the success of the above plastic operations following sympathectomy, to the improvement in the circulation of the feet caused by sympathectomy. In spite of that, one might wonder if, and how much, the sympathectomy causes the healing of those wounds, or whether it is the obligatory rest in bed of the patients, causing the limb to repose in the elevated position in which, as a rule, it is placed. The answer to this question is somewhat difficult.

Without refusing to acknowledge the beneficial effect of sympathectomy in the cure of such ulcerations, we agree more as to the results of rest, for the following reasons: (1) Because we have seen the cure of such ulcerations to take place on medical patients who were simply obliged to stay in bed without undergoing any other treatment; (2) we have had cases of ulcerations on both legs, in which sympathectomy was done on one. In those cases we observed that both limbs were cured in almost the same period of time; and (3) we have also noticed a case in which both feet were ulcerated. The sympathectomy on the right foot did not heal the ulcerations on the left, which were, however, completely cured after the patient had stayed one month in bed.

CONCLUSIONS

The operation of the lumbar block sympathectomy upon "trench feet" may be considered, in general, as a satisfactory operation. Its success being steady, but temporary, as far as pains and the vasometric troubles are concerned, seems doubtful and uncertain for the healing of ulcerations as also in other circulation and neurotrophic troubles.

LIGATURE CARRIER FOR VAGINAL HYSTERECTOMY

ROBERT TAUBER, M.D.
PHILADELPHIA, PA.

ASSOCIATE IN GYNECOLOGY-OBSTETRICS IN THE GRADUATE SCHOOL OF MEDICINE OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

IN PERFORMING a vaginal hysterectomy most surgeons use a needle and needle-holder for ligating the uterine ligaments, vessels, and adnexa. The needle, however, frequently tears the rubber gloves and pricks the finger. To overcome this accident, pointless needles have been recommended; it is also possible to grasp the needle close to the needle point instead of the needle eye and to use the inverted needle combined with the needle-holder like a ligature carrier.

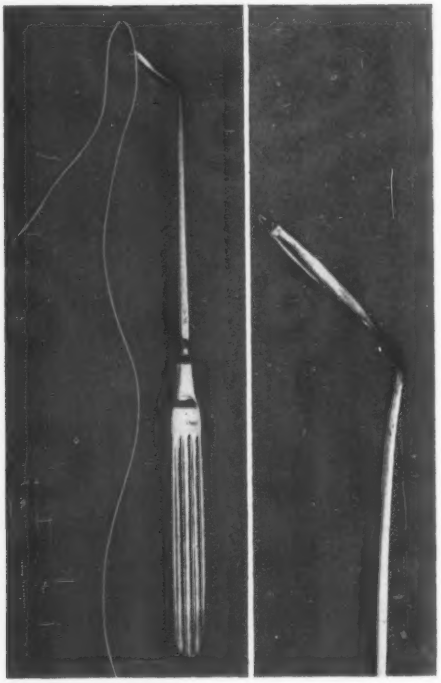


FIG. 1 FIG. 2

FIG. 1.—The portion of the ligature in the concavity of the carrier's head is three times as long as in the convexity.

FIG. 2.—The transverse curve close behind the eye permits catching the ligature as soon as it becomes visible.

The use of needle and needle-holder, however, is complicated at times by needle breakage and improper needle fixation. The usual ligature carrier eliminates these inconveniences, but in performing vaginal hysterectomy this carrier has the following disadvantages: (1) The eye is too distant from the needle point and the oval shape of the big eye makes it necessary to pass a long part

of the instrument before the ligature becomes visible; and (2) the usual carrier has a longitudinal groove starting from the eye and running in the axis of the needle. (3) The ligature often lodges in the groove and cannot be grasped easily, furthermore, the groove causes a sharp edge at the eye and spoils the ligature; and (4) the angle between the needle and the handle of the usual carrier is 90 degrees, which makes it very difficult to apply ligatures to both sides of the uterus.

The following modifications are suggested for the ligature-carrier for performance of a vaginal hysterectomy:

1. The angle between the curved needle and the handle is 45 instead of 90 degrees (Fig. 1). This makes it much easier to place the ligatures to either side of the uterus.

2. The eye is circular and small (Fig. 2). The placing of the eye extremely close to the needle point permits catching the ligature immediately after passing the point of the instrument.

3. The edges of the eye are dull in order to avoid damage to the ligature.

4. There is no longitudinal groove following the eye, which hides the ligature. Instead, a transverse groove is placed close behind the eye (Fig. 2), which permits catching the ligature as soon as it becomes visible. A small, blunt, rectangular hook which fits into the transverse groove is very useful for this maneuver. Instead of the hook a toothless forceps can be used.

A small, but important, technical detail should be emphasized for the application of ligatures with a carrier. The eye divides the ligature into two portions (Fig. 1). These portions should not be equal in length, so that only a small portion of the ligature has to be pulled through the eye in order to disengage the ligature from the carrier. This prevents tangling and damaging of the suture material. The portion of the ligature in the concavity of the carrier's head should be three times as long as the portion on the convexity (Fig. 1). Another point is that the hook, or the forceps, which catches the ligature should not pull on it. Holding the instrument still after catching the ligature, the mere retraction of the ligature carrier will disengage the ligature with the least injury to the suture material.

SOLITARY EOSINOPHILIC GRANULOMA OF RIB

CASE REPORT

LT. COL. B. G. P. SHAFIROFF, M.C., AND MAJOR L. SCHEMAN, M.C.

BROOKLYN, N. Y.

EOSINOPHILIC GRANULOMA of bone is claimed to be an acute manifestation of a basic disease process associated with such chronic variants as nonlipoid histiocytosis (Letterer-Siwe disease) and lipogranulomatosis (Schuller-Christian disease[1]). It is characterized by single or multiple destructive lesions in the bony skeleton except those of the hands and feet, by a localizing symptomatology and by a well-defined histopathology. The diagnostic importance of this condition and its increasing incidence justify the present case report.

Case Report.—A male, age 31, was transferred to our hospital with the diagnosis: "Other diseases of bone, osteolytic lesion of 6th rib, right posterior axillary line, duration two months, cause undetermined." On admission, the patient complained of pain in the anterior side of the right chest near the sternum at the level of the 6th rib. At rest, the pain was vague and ill-defined but with movement of the right arm, became sharp and lancinating and was referred then to the posterior chest. The past medical history was noncontributory even after the final diagnosis was established. Physical examination was within normal limits except for point tenderness over the 6th rib posteriorly just lateral to the medial border of the scapula when the arm was held in acute adduction.

Laboratory Data.—The Wassermann and Kahn tests were negative. Blood count and differential smear were normal in each of four examinations. Sedimentation time (Wintrobe method) was 11 mm. and 14 mm. for 60 minutes. The hematocrit cell volume averaged 46 per cent. The blood chemistry for phosphorus was 4.2 mg. per cent, for calcium 9 mg. per cent, and for serum phosphatase, 5 per cent. Urinalysis was negative for Bence-Jones protein. Temperature, pulse and respiration while in the hospital were normal.

A variety of roentgenologic studies were made in this case. The initial study revealed an osteolytic lesion, 2 cm. in length, located on the posterior axillary line of the 6th rib, suggestive of malignancy, myeloma or osteomyelitis. Roentgenograms of the entire bony skeleton failed to reveal a similar lesion anywhere else. Roentgenologic studies of the gastro-intestinal tract, the genito-urinary tract and the lungs were negative for a primary malignant tumor in these systems. Follow-up roentgenograms of the involved rib showed it to be a slowly growing, irregularly destructive process which after four weeks of observation began to show evidence of mild periosteal reaction, some areas of bony condensation and, finally, fracture through the site of pathology.

In the differential diagnosis, Ewing's tumor, primary myeloma, osteitis fibrosa cystica, metastatic carcinoma, osteogenic sarcoma, osteomyelitis, syphilis and tuberculosis of the rib were considered. The location of the lesion in the bony shaft, the lack of periosteal reaction, the failure to discover a primary focus of malignant tumor and the laboratory data served to exclude it from the neoplastic group. In a like manner, the usual inflammatory conditions of bone such as osteomyelitis, tuberculosis and syphilis were eliminated. Thus, there remained for diagnosis the more unusual pathologic entities of which only fibrous dysplasia and eosinophilic granuloma of bone merited consideration. The well-being of the patient clinically and the absence of major constitutional manifestations further supported the view in favor of a simple benign lesion.

Five weeks after admission to the hospital, and approximately three months after the onset of symptoms, the involved area of the 6th rib was resected. At operation, a

healing pathologic fracture was noted. The rib appeared eroded and filled with a yellow granular tissue. The disease process was localized to the rib. The surrounding tissues, both superficial and deep, were not involved in the pathologic process.

Microscopic sections through the rib showed areas of normal rib and a good deal of new bone formation, resulting in girate patterns. The intertrabecular tissue was

FIG. 1.—Eosinophilic granuloma in rib. The lesion is irregularly destructive with areas of bony condensation along the edges of the process.

loose, fibrillary, highly vascularized and contained a few marrow cells. Nearer to the periphery there were large collections of eosinophils, many of which were mononuclear, while others were polymorphonuclear. Interspersed among the latter arranged in sheets, strands and nests, were large, pale-pink staining cells (histiocytes) with elongated or indented nuclei. *Pathologic Diagnosis:* Eosinophilic granuloma.

Eosinophilic granuloma of bone is rapidly assuming importance as a specific clinical entity. Although originally described as a disease of the very young[2] it is also found to exist in the adult. Its relationship to virus infection or trauma remains to be determined. The underlying cellular pathology of

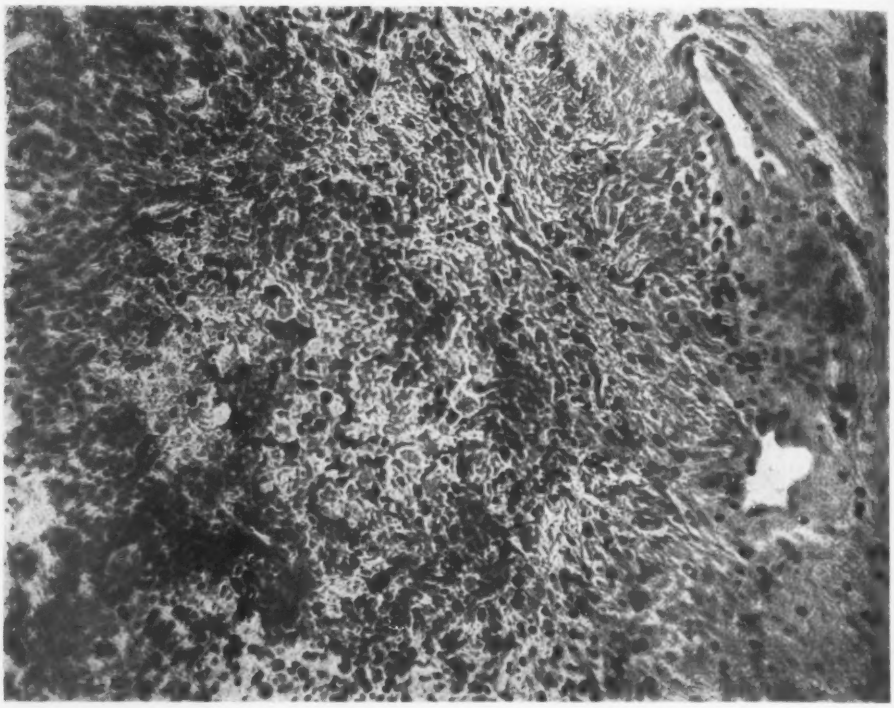


FIG. 2.—Microscopic section from lesion showing concentration of eosinophils with some histiocytes.

histiocytosis and eosinophilic granuloma is also present in nonlipoid histiocytosis and lipogranulomatosis of bone. Hence, the belief that eosinophilic granuloma is an acute variant of the latter two chronic conditions. Treatment is not specific, since this is a self-limiting, spontaneously regressing disease, which is best treated in conformity with general surgical principles.

REFERENCES

[1] Jaffe, H. L., and Lichtenstein, L.: Arch. Path., 37, 91, 1945.
[2] Green, W. T., and Farber, S. J.: J. Bone and Joint Surg., 30, 499, 1942.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.